Perioperative Management of Direct Oral Anticoagulants (DOACs): A Systemic Review

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Tagore Sunkara[1], Emmanuel Ofori[1], Vadim Zarubin[2], Megan E. Caughey[3], Vinaya Gaduputi[4] and Madhavi Reddy[1]

[1]Division of Gastroenterology, The Brooklyn Hospital Center, Brooklyn, NY, USA. [2]Division of Hematology and Oncology, The Brooklyn Hospital Center, Brooklyn, NY, USA. [3]New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY, USA. [4]SBH Health System, Bronx, NY, USA.

ABSTRACT: Direct oral anticoagulants (DOACs) are in wide use among patients requiring both short- and long-term anticoagulation, mainly due to their ease of use and the lack of monitoring requirements. With growing use of DOACs, it is imperative that physicians be able to manage patients on these medications, especially in the perioperative period. We aim to provide guidance on the management of DOACs in the perioperative period. In this review, we performed an extensive literature search summarizing the management of patients on direct-acting anticoagulants in the perioperative period. A total of four direct-acting oral anticoagulants were considered appropriate for inclusion in this review. The drugs were dabigatran etexilate mesylate (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa). Management of patients on DOACs in the perioperative period involves an assessment of thromboembolic event risk while off anticoagulation compared to the relative risk of bleeding if such drug is continued. DOACs may not need to be discontinued in minor surgeries or procedures, and in major surgeries, they may be discontinued hours prior depending on drug pharmacokinetics and renal function of the patients.

KEYWORDS: direct oral anticoagulants, new oral anticoagulants, DOACs

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CORRESPONDENCE: tagoresunkara@hotmail.com

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Introduction

Direct oral anticoagulants (DOACs) are in wide use among patients requiring both short-and long-term anticoagulation. DOACs are preferred because of the ease of use, favorable pharmacokinetics with fixed dosing, decreased drug–drug interactions, and the lack of monitoring requirements.[1] With growing use of DOACs, it is imperative that physicians be able to manage patients on these medications in the perioperative period, while balancing the risk of bleeding with that of thromboembolic events. In this review, we aim to discuss in detail the mechanism of action, pharmacokinetics, indications, dosages, drug interactions, and indications of each DOAC. Additionally, we discuss the side effects, contraindications, and most importantly, the perioperative management of patients on each DOAC.

Management of patients on DOACs in the perioperative period involves an assessment of thromboembolic event risk while off anticoagulation compared to the relative risk of bleeding if such drug is continued. As with warfarin, in minor surgeries or procedures, DOACs may not need to be discontinued, although evidence to support such practice is not robust.[2] In cases where DOACs are to be stopped prior to the procedure, advance planning and coordination is required. The goal of perioperative DOAC interruption is to seek minimal or no residual anticoagulant effect at the time of procedure.[3] Procedures are therefore performed outside of peak systemic drug levels.[4] Given the relative short half-life of DOACs, anticoagulant interruption is usually safe, with shorter durations in patients with normal renal and hepatic functions.[5] In determining the time of anticoagulant interruption, various factors are considered, including the elimination half-life of the DOAC, renal function of the patient (calculated creatinine clearance (CrCl)) and its corresponding effect on DOAC excretion, bleeding risk associated with the planned procedure, and the type of anesthesia.[3]

Major bleeding as defined by the International Society on Thrombosis and Haemostasis for surgical studies is bleeding that is fatal or in a critical organ; extra surgical site bleeding with a decrease in hemoglobin of ≥ 2 g/dL or requiring transfusion of ≥ 2 units of blood; and surgical site bleeding that requires second intervention or causes hemarthrosis with delayed mobilization or wound healing, prolonged hospitalization, or deep wound infection or that is unexpected

and prolonged and causes hemodynamic instability.[6] Conversely, arterial thromboembolic events are characterized as major in the form of ischemic stroke or systemic embolism and considered minor in the form of a transient ischemic attack. Minor bleeding is therefore defined as bleeding that does not meet the criteria for major bleeding.[6]

Thromboembolic risks during anticoagulant interruption are dependent on the presence of underlying comorbid conditions such as atrial fibrillation, prosthetic heart valves, and recent venous or arterial thromboembolism in the preceding three months.[2] Very high thrombotic risk individuals are those with mitral valve prostheses, recent stroke or transient ischemic attack within the past six months, CHA_2DS_2-VASc score of ≥ 6, rheumatic valvular heart disease, recent venous thromboembolism (VTE) within the past three months, or severe thrombophilia.[2] Individuals at high thrombotic risk in the perioperative period include those with bileaflet aortic valve prosthesis with either atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age > 75 years, CHA_2DS_2-VASc score of 4–5, VTE within prior 3 to 12 months, and active malignancy. Moderate thrombotic risk individuals are those with bileaflet aortic valve prosthesis without atrial fibrillation, CHA_2DS_2-VASc score of 2–3, and VTE more than 12 months prior.[2]

Bleeding risk is determined by the invasiveness and timeliness of the procedure or surgery. Increased bleeding risk procedures are considered as having 2%–4% two-day risk of major bleeding while low-risk procedures have 0%–2% bleeding risk.[7] Increased bleeding risk procedures include, but not limited to, vascular surgery, general surgery, bilateral knee replacement, endoscopically guided fine-needle aspiration, polypectomy, variceal treatment, biliary sphincterotomy, pneumatic dilatation, transurethral prostate resection, and any major surgery lasting over 45 minutes duration.[5] Low bleeding risk procedures include abdominal hernia repair, abdominal hysterectomy, axillary node dissection, and bronchoscopy with or without biopsy.[5] Cataract eye surgery, cholecystectomy, dilatation and curettage, gastrointestinal endoscopy with or without biopsy, enteroscopy, biliary or pancreatic stent placement without sphincterotomy, endoscopic ultrasound without fine-needle aspiration, hemorrhoidal surgery, and tooth extractions are also considered low-risk procedures.[5]

Patients with high risk of bleeding in the perioperative period require interruption in their anticoagulation but stand an increased risk of thromboembolic complications. Individuals with very high thromboembolic risk such as those with recent ischemic cerebrovascular accidents are recommended to delay elective surgery or invasive procedures until the thromboembolic risk has decreased to baseline.[8] Additionally, individuals with atrial fibrillation with suboptimal anticoagulation in the month prior to surgery are recommended to postpone such surgery in order to decrease the relative thrombotic risk.[9]

Materials and Methods

We conducted an extensive English literature search using Pubmed, Medline, UptoDate, Medscape, and Google to identify peer-reviewed original research and review articles using the keywords "direct-acting oral anticoagulants", "new oral anticoagulants", and "DOACs". The search period included articles published until August 2016. We selected studies involving human subjects and manually searched the references to identify additional relevant studies. Inclusion criterion for evaluation was the perioperative management of direct-acting oral anticoagulants.

Results

A total of four direct-acting oral anticoagulants were considered appropriate for inclusion in this review. These drugs were dabigatran etexilate mesylate (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa). All drugs are summarized in Table 1.

Dabigatran etexilate mesylate (Pradaxa).

Mechanism of action. Dabigatran etexilate mesylate, known by the brand name Pradaxa, is an oral anticoagulant that directly binds to thrombin's active site, inhibiting both free and clot-bound thrombin. Dabigatran competitively inhibits thrombin, preventing it from converting fibrinogen to fibrin monomers during the coagulation cascade.[10] Although in its prodrug formulation, dabigatran etexilate does not produce anticoagulation effects, it is converted in vivo to dabigatran, an active compound that does. This active compound is responsible for blocking thrombin-mediated events, including the degradation of fibrinogen, stimulation of factors V, VIII, XI, and XIII, and platelet aggregation.[11] Till date, there are no specific tests available to monitor dabigatran activity.

Pharmacokinetics. Dabigatran is absorbed quickly through an oral means of administration. In the context of postoperative use, however, absorption initially occurs at a much slower rate. Dabigatran has a rapid but also a predictable therapeutic effect, hence requiring less constant monitoring.[10] With protein binding of 35%, 50–70-L volume of distribution, and bioavailability of 3%–7%, dabigatran reaches plasma peak concentration within one hour if taken alone and by two hours if consumed with food.[11]

The half-life of dabigatran ranges from 12 to 17 hours. It is important to note that the half-life approaches 14–17 hours in elderly individuals. In patients with mild-to-moderate renal impairment (CrCl of 30–60 mL/minute), the half-life is between 15 and 18 hours, whereas in those with severe renal impairment (CrCl < 30 mL/minute), it can last as long as 28 hours.[12] Dabigatran undergoes hepatic metabolism. Hepatic esterase hydrolyzes the inactive dabigatran etexilate to its active form, dabigatran. It is a substrate of the efflux transporter P-glycoprotein but has no interaction with the CYP450 enzymes. Nearly 80% of dabigatran is excreted in the urine.[13]

Indications, dosage, and drug interactions. Dabigatran was the first oral direct thrombin inhibitor approved by the FDA in 2010 to prevent stroke in those with nonvalvular atrial fibrillation.[10] It is recommended for use in patients who have CrCl of at least 15 mL/minute. Dabigatran is also used to prevent deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who have previously been treated with a parenteral anticoagulant for 5–10 days or who have recently undergone hip or knee replacement surgery. Ultimately, dabigatran is thought to be a possible alternative to warfarin in individuals who may necessitate long-term anticoagulation.[11] Dabigatran is an oral anticoagulant that is administered in dosages of 75 and 150 mg twice daily. In patients with nonvalvular atrial fibrillation undergoing stroke prophylaxis and prevention of systemic embolism, with a CrCl of greater than 30 mL/minute, 150 mg of dabigatran twice daily is recommended. Stangier et al[14] recommended 75 mg of dabigatran twice daily for patients with CrCl of 15–30 mL/minute. If the CrCl is less than 15 mL/minute, the drug is not recommended.

Similarly, with DVT and PE treatment, and in patients with a CrCl of greater than 30 mL/minute, 150 mg of dabigatran twice daily is recommended. If CrCl is less than 30 mL/minute, the drug is not recommended.[11] In patients who underwent hip or knee replacement surgery with CrCl greater than 30 mL/minute, dabigatran is recommended for VTE prophylaxis. A total of 110 mg of dabigatran taken one to four hours after surgery, followed by 220 mg once daily for 4–5 weeks for hip replacement and for 10 days for knee replacement is recommended.

Although not an inducer, inhibitor, or substrate of CYP450 enzymes, dabigatran is a substrate of the efflux transporter P-glycoprotein. P-glycoprotein inducers, like rifampin and carbamazepine, lessen the extent of dabigatran exposure, preventing the drug from achieving its full effect. These inducers should most often be discontinued when using dabigatran to treat nonvalvular atrial fibrillation, postoperative thromboprophylaxis, DVT, or PE.[13]

P-glycoprotein inhibitors have an opposite impact, thus increasing the level of dabigatran exposure. P-glycoprotein inhibitors like amiodarone, clarithromycin, dronedarone, quinidine, and verapamil enhance dabigatran exposure and further magnify in patients with renal impairment. Thus, the recommendation is to avoid the simultaneous use of dabigatran and P-glycoprotein inhibitors in patients with a CrCl of less than 50 mL/minute when treating DVT, PE, and postoperative thromboprophylaxis. The recommendation is also to avoid inhibitors in patients with a CrCl of less than 30 mL/minute when treating for nonvalvular atrial fibrillation.[11]

Generally, using dabigatran in conjunction with other anticoagulants such as unfractionated heparin for bridging may increase the risk of bleeding due to an enhanced anticoagulation effect during the perioperative period. Acenocoumarol and warfarin are however exceptions and are safer choices because they act on vitamin K and might be most useful in transition or bridging periods. Since food does not affect the bioavailability of dabigatran, it can be taken without regard to meals. Doing so, however, will slow achieving a peak plasma concentration by two hours.[11]

Side effects and contraindications. Two important considerations with dabigatran include the possibilities of an adverse thrombotic event or a spinal hematoma. Dabigatran should only be abruptly discontinued in the event of pathological bleeding, and in such a scenario, another anticoagulant should be used during that time to prevent a thrombotic event if the risk of thrombosis is high, after weighing the risk/benefit ratio. Furthermore, patients receiving dabigatran must be particularly cautious with neuraxial anesthesia and spinal punctures, as with most anticoagulants, the greatest concern is hemorrhage. One of the major side effects of anticoagulants is active pathological bleeding. This is especially an issue within the context of the new oral anticoagulation drugs, because with exception of dabigatran, all others do not possess their own specific antidote.

In October 2015, an antidote for dabigatran known as idarucizumab (Praxbind) was approved by FDA. Idarucizumab is a humanized monoclonal antibiotic fragment that is capable of reversing anticoagulation by binding dabigatran. It can be used to diminish serious bleeding in patients who take dabigatran and to reverse anticoagulation effect in patients who might need to undergo an emergent/urgent surgical procedure.[15] Idarucizumab is available in the form of a 2.5 g/50 mL vial solution. Its mechanism of action involves binding dabigatran and its acylglucuronide metabolites with a higher affinity than the dabigatran is able to bind to the thrombin. This then neutralizes the dabigatran, preventing it from producing an anticoagulation state. Idarucizumab has a half-life of 47 minutes to 10.3 hours and is cleared at a rate of 47 mL/minute. It is excreted in urine, and 32.1% of the time, this occurs within six hours. This drug can also be used to control instances of dire, uncontrolled bleeding that could otherwise be fatal in those on dabigatran.

Research suggest that 5 g of idarucizumab administered intravenously (IV) is an effective dose. In those with renal impairment, this dosage does not need to be adjusted; however, it is less clear in those with hepatic impairment. Some of the most common adverse effects of idarucizumab include hypokalemia, delirium, constipation, pyrexia, pneumonia, headache, thromboembolic events, and hypersensitivity. Idarucizumab should not be taken with any other drugs, but when administered, should be given as a 5-g IV dose through two consecutive 2.5-g infusions.[15] Finally, dabigatran is contraindicated in those with mechanical heart valves. The RE-ALIGN study found that those with mechanical heart valves who received dabigatran experienced more thromboembolic complications compared to warfarin.[16] Dabigatran is also contraindicated in those with a CrCl of less than 30 mL/minute and in pregnant women. This drug is a pregnancy category C because as a small molecule, it is able to travel across the placenta.[17]

Table 1. Comprehensive overview of direct oral anticoagulants (DOACs).

DRUG	TRADE NAME	MECHANISM OF ACTION	PHARMACOKINETICS			INDICATIONS	DOSE (mg)
			ROUTE OF ADMINISTRATION	HALF LIFE (hr)	PEAK CONCENTRATION (hr)		
Dabigatran etexilate mesylate	Pradaxa	Direct thrombin inhibitor. Target—factor II	Oral	12–17	2–3	Reduce risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation; Treatment of deep venous thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5–10 days Reduce risk of recurrence of deep venous thrombosis and pulmonary embolism in patients who have been previously treated. Prophylaxis of deep vein thrombosis and pulmonary embolism in patients who have undergone hip replacement surgery	75/150
Rivaroxaban	Xarelto	Direct factor Xa inhibitor	Oral	7–13	2–4	Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. Reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Treatment of DVT and PE. Reduce the risk of recurrence of DVT and PE following initial 6 months treatment for DVT and/or PE.	10/15/20
Apixaban	Eliquis	Direct factor Xa inhibitor	Oral	12	1–4	Reduce risk of stroke in patients with non-valvular atrial fibrillation Treatment of deep venous thrombosis and pulmonary embolism Post op prophylaxis for DVT/PE prevention following hip or knee replacement surgery	2.5/5

DRUG INTERACTIONS	SIDE EFFECTS	CONTRAINDICATIONS	CATEGORY	ANTIDOTE	PERI-OPERATIVE MANAGEMENT	
					FOR PROCEDURES	FOR ENDOSCOPY
Decreased availability with P-glycoprotein pump inducers, fatty food and PPI. Increased availability with P-glycoprotein pump inhibitors	GI upset GI bleed Throbocytopenia Hypersensitivity	Active pathological bleed Prior reaction to pradaxa Mechanical prosthetic heart valve CrCl < 30	C	Idarucizumab—Praxbind	If possible, discontinue dabigatran 1 to 2 days (CrCl ≥ 50 mL/min) or 3 to 5 days (CrCl < 50 mL/min) before invasive or surgical procedures due to increased risk of bleeding. Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required. Restart dabigatran promptly following surgery	Irrespective of CrCl, discontinue 24 hours prior to low bleeding risk procedure. In high risk bleeding risk procedures, discontinue 48–72 hours prior (CrCl > 50 mL/min). Discontinue 72 to 96 hours before high risk endoscopic procedure(CrCl 30–49 mL/min) If severe renal impairment (CrCl < 29 mL/min), discontinue 96 to 144 hours before endoscopy.
Inhibitors of CYP 3A4 and P-glycoprotein transporter. HIV protease inhibitors Azoles	Bleeding Thrombocytopenia Agranulocytosis Hepatitis Pruritus Stevens-Johnson Syndrome Hypersensitivity	Active pathological bleed Prior reaction to Pradaxa Child-Pugh B-C Liver disease with coagulopathy CrCl < 15	C	Andexanet alfa (FDA review)	Stop rivaroxaban at least 24 hours before procedure. Restart rivaroxaban after surgery/procedure as soon as adequate hemostasis is established. If unable to take oral medication following surgical intervention, consider administering a parenteral drug	If CrCl > 90, discontinue 24 hours before procedure If CrCl 60–90, discontinue 48 hours before procedure If CrCl 30–59, discontinue 72 hours before procedure, If CrCl 15–29, discontinue 96 hours before procedure
HIV protease inhibitors Azoles Rifampin Phenytoin Carbamazepine Phenobarbitol	Bleeding Syncope Hypersensitivity	Active pathological bleed Prior reaction to Pradaxa Child-Pugh B-C Liver disease with coagulopathy CrCl < 15	B	Charcoal (if last intake within 2–3 hours) Non-activated PCC or activated PCC	Discontinue at least 48 hours before elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Discontinue at least 24 hours before elective surgery or invasive procedures with low risk of unacceptable or where the bleeding would be noncritical in location and easily controlled	If CrCl > 60, discontinue 24–48 hours before procedure If CrCl 30–59, discontinue 72 hours before procedure If CrCl 15–29, discontinue 96 hours before procedure

(*Continued*)

Table 1. (*Continued*)

DRUG	TRADE NAME	MECHANISM OF ACTION	PHARMACOKINETICS			INDICATIONS	DOSE (mg)
			ROUTE OF ADMINISTRATION	HALF LIFE (hr)	PEAK CONCENTRATION (hr)		
Edoxaban	Savaysa	Direct factor Xa inhibitor	Oral	9–11	1–2	Reduce risk of stroke and systemic embolism associated with nonvalvular atrial fibrillation Treatment of deep vein thrombosis (DVT) and pulmonary embolus (PE) in patients who have been initially treated with a parenteral anticoagulant for 5–10 days	15/30/60

One notable side effect of dabigatran is dyspepsia, which has been reported in up to 10% of patients. Although gastrointestinal upset can be improved with time and by consuming food with dabigatran, dyspepsia effect distinguishes the drug from rivaroxaban, apixaban, and edoxaban. Other side effects from postmarketing reports include angioedema, esophageal ulcers, thrombocytopenia, and hypersensitivity reactions.[13]

Perioperative management of patients on dabigatran. Dabigatran facilitates a shorter interruption of oral anticoagulation with comparable periprocedure bleeding risk. In the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial with a total of 4,591 patients, who underwent elective procedures or surgery, Healey et al[18] reported the perioperative thromboembolic risk of 1.2% in the form of cerebrovascular accidents, cardiovascular death, and pulmonary embolus among subjects who received dabigatran, which was similar for patients on warfarin. Schulman et al[19] in the RE-COVER II trial reported major bleeding incidence rate of 1.8% among their study population treated with dabigatran compared with patients on vitamin K antagonist interrupted for surgery (2.94%). Dabigatran and warfarin were associated with similar rates of periprocedural bleeding, including patients having urgent surgery.

Dabigatran is recommended to be discontinued 24 hours prior to endoscopic procedures, irrespective of renal functional status in low bleeding risk procedures. In high bleeding risk procedures or surgeries, dabigatran is recommended to be discontinued 48–72 hours prior in normal renal function and mild renal function (CrCl $>$ 50 mL/minute). In moderate renal impairment (CrCl of 30–49 mL/minute), discontinue 72–96 hours before high-risk endoscopic procedure. If severe renal impairment (CrCl $<$ 29 mL/minute), discontinue 96–144 hours before endoscopy.[20] Among patients undergoing invasive procedures with increased risk of bleeding, dabigatran is recommended to be discontinued 24–48 hours in normal or mild renal impairment (CrCl $\geq$ 50 mL/minute) and 72–120 hours in patients with moderate renal impairment (CrCl of 30–49 mL/minute) prior due to increased risk of bleeding. Acosta et al[20] recommended discontinuation of dabigatran for a longer period of time in patients undergoing major surgeries, spinal puncture, or procedures that involve placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required. According to Schulman et al,[19] an interval of 24–96 hours between the last dose of dabigatran and the planned surgery or an invasive procedure was sufficient for the vast majority of patients. In low bleeding risk procedures, DOACs need not be interrupted.

Preoperatively, bridging anticoagulant therapy with unfractionated heparin or low molecular weight heparin is employed in very high-risk thromboembolic patients who require longer duration of anticoagulant interruption for reasons including renal insufficiency. Postoperative resumption of dabigatran should be done when hemostasis is thought to be achieved following surgery.[20] Given its rapid onset and peak level within 2–3 hours after intake, it is recommended to resume dabigatran between 48–72 hours after high bleeding risk procedure and 24 hours in a low bleeding risk procedure.

Rivaroxaban (Xarelto).

Mechanism of action. Rivaroxaban, known by the brand name Xarelto, is an oral anticoagulant that prevents fibrin clot formation by directly inhibiting factor Xa, which is a part of the prothrombinase complex, and in doing so, inactivates platelets and the degradation of fibrinogen to fibrin.[21] Rivaroxaban does not require a cofactor and is known to prolong prothrombin time (PT), partial thromboplastin time (aPTT), and HepTest.[22] The most accurate means of measuring rivaroxaban levels in the blood is to perform a calibrated anti-Xa assay.[17]

Pharmacokinetics. Rivaroxaban is administered orally and rapidly absorbed. With a protein binding of 92%–95%, rivaroxaban is largely albumin bound. Its volume of distribution is around 50 L, and its bioavailability is dose dependent. A 10-mg dose corresponds to a bioavailability of between 80%

DRUG INTERACTIONS	SIDE EFFECTS	CONTRAINDICATIONS	CATEGORY	ANTIDOTE	PERI-OPERATIVE MANAGEMENT	
					FOR PROCEDURES	FOR ENDOSCOPY
HIV protease inhibitors Cyclosporine Rifampin ASA/NSAIDs	Bleeding Anemia Rash Abnormal liver function tests	Active pathological bleed Prior reaction to Pradaxa Child-Pugh B-C Liver disease with coagulopathy CrCl < 15 or CrCl > 95	C	Charcoal (if last intake within 2–3 hours) Non-activated PCC or activated PCC	Discontinue 2–3 days prior and bridge with unfractionated heparin if the risk of thromboembolism is high. Discontinue 72 hours prior to high bleeding risk procures. Discontinue at least 24 hours prior to low bleeding risk procedures.	Discontinued least 24 hours before procedure in CrCl 15–90. No data exists for discontinuation in CrCl < 15

and 100%, whereas a 20-mg dose results in one of around 66%. Rivaroxaban achieves peak concentration within the plasma by two to four hours. The half-life of this drug is usually between 5 and 9 hours, except in the elderly, in which case, the half-life lasts between 11 and 13 hours. Rivaroxaban undergoes hepatic metabolism, through CYP3A4 and CYP2J2 enzymes, and is excreted, as both an unchanged drug and as inactive metabolites, 66% through the urine and 28% through the feces.[21] Rivaroxaban is a substrate of both ABCG2 and P-glycoprotein efflux transporter proteins.[22]

Indications, dosage, and drug interactions. Rivaroxaban dosages occur in 10, 15, and 20 mg tablets. A 20 mg/day oral dose with dinner is used to protect against stroke and systemic embolism in patients with nonvalvular atrial fibrillation whose CrCl is > 50 mL/minute. If CrCl is between 15 and 50 mL/minute, the dose recommended is 15 mg/day with dinner. Rivaroxaban is also used as prophylaxis against DVT and PE at a dose of 10 mg orally daily for 12 days and a dose of 10 mg orally daily for 35 days in instances of knee replacement surgery and hip replacement surgery, respectively. In this setting, it is important to administer the first dose between 6 and 10 hours after surgery to ensure that homeostasis has been reached, thereby reducing the likelihood of complications following surgery.

Another unique application of rivaroxaban is that it can be used both to treat a DVT or PE and to prevent recurrent instances of both. To treat DVT or PE, rivaroxaban is prescribed for 21 days at a dose of 15 mg orally every 12 hours, followed by a dose of 20 mg orally daily for 3 months. Finally, to reduce the risk of recurrent episodes of DVT and PE, patients are advised to take rivaroxaban 20 mg orally daily for an extended period.[22] Rivaroxaban is always recommended to be taken with food.

Rivaroxaban is metabolized through both oxidative degradation and hydrolysis. The process of oxidative degradation is catalyzed by CYP3A4/5 (major) and CYP2J2 (minor). As a result, drugs that inhibit cytochrome P450 (CYP) 3A4 will hinder the removal of rivaroxaban, causing an elevation in the drug level.[23] Rivaroxaban is also a substrate of P-glycoprotein and ABCG2 efflux transporter.[22] Rivaroxaban is largely protein bound, and a drug that inhibits both CYP3A4 and P-glycoprotein, like ketoconazole, will produce a maximal increased rivaroxaban effect.[10] Strong CYP3A4 inducers and inhibitors are categorized as Risk X, which means that they should avoid being taken in combination with rivaroxaban. Moderate CYP3A4 inducers are categorized as Risk C and can be taken in combination with rivaroxaban, but must be monitored very closely. Moderate CYP3A4 inhibitors and P-glycoprotein substrates are categorized as Risk D. This means that in patients with normal renal function, no adjustment needs to be made. However, in those with a CrCl of 15–80 mL/minute, it is best to consider therapy modification and only use these drugs in combination if benefits outweigh risks.

More specifically, the following drugs are considered Risk X in combination with rivaroxaban: most anticoagulants (excluding acenocoumarol and warfarin), apixaban, dabigatran etexilate, edoxaban, hemin, omacetaxine, St. John's wort, urokinase, and vorapaxar. Many of these are contraindicated with rivaroxaban because they, too, act as anticoagulants and might increase the likelihood of an acute bleeding event.[21] The interaction between rivaroxaban and drugs like ketoconazole and HIV protease inhibitors (indinavir and ritonavir) is so serious that it is recommended as an alternative therapy.[22]

Side effects and contraindications. For each category of treatment (nonvalvular AF, thromboprophylaxis following orthopedic surgery, and protection against recurrent DVT or PE), there are specific guidelines for how dosages should be modified within the context of renal impairment as mentioned above with dosing. Generally, rivaroxaban should be avoided in those with acute renal failure, severe renal impairment, or a CrCl of less than 15 mL/minute. The pharmacodynamics of hepatic impairment and rivaroxaban has been

researched less; however, as a general rule, it is best to avoid use in patients with moderate-to-severe levels of impairment (Child-Pugh B and C) or liver disease with coagulopathy.[22]

As previously discussed, the major issue with anticoagulation is bleeding. Rivaroxaban remains no exception to this, and a contraindication of the drug is active pathological bleeding. With that said, the EINSTEIN studies discovered that major bleeding occurred less in patients given rivaroxaban compared to patients receiving the standard anticoagulation. This difference was most apparent with intracranial bleeding. There is no antidote to rivaroxaban, but it is speculated that, pending additional research, prothrombin complex concentrates might be helpful in some instances of bleeding complications.[24]

Much like dabigatran and edoxaban, rivaroxaban is a pregnancy category C drug, which means that it is contraindicated in pregnancy. Aside from bleeding, some of the additional side effects of rivaroxaban include the following: dizziness (6%), peripheral edema (6%), hypersensitivity reactions or rash (2%), syncope (2%), and though more rare, thrombocytopenia, agranulocytosis, hepatitis, pruritis, and Stevens–Johnson syndrome.[22]

Perioperative management of patients on rivaroxaban. Rivaroxaban has lower thromboembolic risk and major bleeding risk. In the ROCKET AF (rivaroxaban once daily, oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) trial, there was 0.3% thromboembolic risk observed among rivaroxaban-interrupted individuals.[9]

Rivaroxaban should be discontinued 48 hours prior to high bleeding risk procedures. Restart rivaroxaban after surgery as soon as adequate hemostasis is established. If unable to take oral medication following surgical intervention, consider bridging with a parenteral low molecular weight heparin (LMWH).[20]

In low bleeding risk surgeries and procedures such as endoscopy, discontinue rivaroxaban 24 hours prior to procedure in patients with normal renal function (CrCl > 90 mL/minute). In mild renal impairment (CrCl of 60–90 mL/minute), discontinue rivaroxaban 48 hours before procedure. If moderate renal impairment (CrCl of 30–59 mL/minute), discontinue rivaroxaban 72 hours before procedure, and if severe renal impairment (CrCl of 15–29 mL/minute), discontinue rivaroxaban 96 hours before procedure.[20]

Rivaroxaban can be restarted at the same prior dose after hemostasis has been reached; however, in high bleeding risk procedures, it is recommended to reinitiate rivaroxaban after 48–72 hours. During such gap without anticoagulation, bridging with LMWH may be required in high and very high thromboembolic risk patients.

Apixaban (Eliquis).

Mechanism of action. Apixaban, known by the brand name Eliquis, is an oral anticoagulant that acts on the same mechanism as rivaroxaban and edoxaban. All three of these drugs directly and selectively inhibit factor Xa, which occupies a pivotal role converting prothrombin to thrombin. This is significant because thrombin is needed both to activate platelets and to produce fibrin from fibrinogen for clot formation.[25] Furthermore, factor Xa is a crucial part of the blood coagulation cascade. The ultimate goal of both the extrinsic and intrinsic pathways is to activate factor X to become factor Xa in order to perpetuate the cascade. By interfering with this important step, apixaban achieves a state of anticoagulation.

Pharmacokinetics. Apixaban is administered orally and displays a more prolonged absorption than dabigatran or rivaroxaban.[26] Thus, apixaban does not reach a peak plasma concentration until three to four hours after administration. Apixaban is 87% protein bound, with a 21-L volume of distribution and a bioavailability of 50%. With repeated dosing, the half-life of apixaban is 12 hours. Apixaban is mostly metabolized by CYP3A4. It is a substrate of P-glycoprotein and breast cancer-resistant protein.[25] A total of 27% of the drug's total clearance occurs through the kidney, and 25% is excreted as metabolites in the urine and feces.[26]

Indications, dosing, and drug interactions. To prevent deep venous thrombosis, apixaban is prescribed in 10 mg doses twice daily for seven days, which is later tapered down to 5 mg twice a day. A dose of 2.5 mg twice daily following six months of a prior initial treatment for DVT has been shown to reliably diminish the risk of a recurrence.

Apixaban also offers protection from stroke and systemic embolism in patients with nonvalvular atrial fibrillation with a dose of 5 mg twice daily. However, if a patient has two of the following characteristics, a dose of 2.5 mg twice daily is considered sufficient: greater than 80 years of age, body weight of less than 60 kg, or a serum creatinine of greater than 1.5 mg/dL. The other indications do not need renal dose adjustments. Apixaban is not recommended in severe liver dysfunction (Child-Pugh C). Treatment for PE with apixaban requires first 10 mg twice daily for seven days and later 5 mg twice daily, whereas reducing recurrence requires just 2.5 mg twice daily after prior treatment.[25] After a recent surgery, 2.5 mg of apixaban twice daily for 35 days (hip replacement) or 12 days (knee replacement) starting 12–24 hours after the surgery has been shown to reduce the risk of a venous thrombus.

Much like rivaroxaban, apixaban is metabolized by the CYP3A4 enzyme. More specifically, apixaban is a substrate of BCRP, CYP1A2 (minor), CYP2C19 (minor), CYP2C8 (minor), CYP2C9 (minor), CYP3A4 (major), and P-glycoprotein. It also weakly inhibits CYP2C19.[25] If a substance inhibits CYP3A4, it will prevent effective metabolism and excretion of apixaban. This will then cause the levels of apixaban to accumulate in the blood.[23] Additionally, if a patient has diminishing renal or hepatic function, this can produce an increased drug effect, even without a CYP3A4 inhibitor.[10]

Some of the drugs that act as inhibitors on cytochrome P450 and increase apixaban's anticoagulation per dose include the following: amiodarone, selective serotonin reuptake inhibitors, and cimetidine. Moderate CYP3A4 inhibitors are

categorized as Risk C when used with apixaban, requiring close monitoring. Strong CYP3A4 inhibitors are also categorized as Risk C, and this category includes the following: cobicistat, darunavir, itraconazole, ketoconazole, lopinavir, ombitasvir, paritaprevir, ritonavir, saquinavir, and telaprevir. Grapefruit juice is also known to dramatically increase levels of apixaban and must be consumed with caution when taking this drug.[25] When administering apixaban with dual inhibitors of both CYP3A4 and P-glycoprotein, it is suggested that the dosage be modified. The dosage should be decreased by 50% if the patient is taking greater than 2.5 mg twice daily, and if taking 2.5 mg twice daily, coadministration of strong dual inhibitors should be avoided all together.[26]

Some of the drugs that act as inducers on cytochrome P450 include the following: carbamazepine, phenytoin, rifampin, and barbiturates. In contrast to the inhibitors, these inducers will enhance the clearance of apixaban, thereby reducing apixaban's therapeutic effect, which could put the patient at risk for forming a clot.[27] Moderate inducers are categorized as Risk C and must be closely monitored; strong inducers are categorized as Risk X, implying that they should not be used in combination with apixaban. Some of the other drugs that are categorized as Risk X with apixaban include anticoagulants (with the exception of acenocoumarol and warfarin), dabigatran etexilate, edoxaban, hemin, omacetaxine, St. John's wort, urokinase, and vorapaxar.[25] Apixiban is also contraindicated with the following medications: carbamazepine, defibrotide, dexamethasone, fosphenytoin, prothrombin complex concentrate (human), rifabutin, rifampin, St. John's wort, and warfarin.[26]

Side effects and contraindications. Bleeding and severe hypersensitivity are major contraindications for the administration of apixaban. More specifically, this drug should not be used in those with a prior reaction to Pradaxa, a Child-Pugh of B or C, liver disease with coagulopathy, or a CrCl of less than 15 mL/minute. Some side effects include bleeding (1.41%–2.13%), syncope (1%), and hypersensitivity reactions, namely, skin rashes or allergic edema (1%).[26]

Perioperative management of patients on apixaban. Apixaban, like the other DOACs, has a lower thromboembolic risk and major bleeding risk. Thromboembolic risk determined in the ARISTOTLE trial (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation) noted 16 thromboembolic events (30-day postprocedural evaluation for stroke or any VTE) out of 4,624 procedures (0.35%) among subjects on apixaban and 26 events out of 4,530 procedures (0.57%) in patients receiving warfarin.[28] Patients with recent thromboembolism had higher risk of the occurrence of an acute preoperative event.

Apixaban-treated patients evaluated in the preoperative setting for major bleeding events 30 days postprocedure in the ARISTOTLE trial had 74/4,560 (1.62%) major bleeding events compared to 86/4,454 (1.93%) events in the warfarin arm. These patients were found to have a similar risk of death in the 30-day postprocedure period accounting for 54/4,624 (1.17%) in the apixaban arm and 49/4,530 (1.08%) in the warfarin arm, which again was not statistically significant. Bleeding risk for patients receiving apixaban was not significant in the preoperative period and patients can safely resume anticoagulation with apixaban, once hemostasis is achieved.[28]

Limited data comparing risks and benefits of apixaban continuation or cessation exist, and thus, every decision is made on a case-by-case basis. Apixaban is recommended to be discontinued 24–48 hours before high bleeding risk procedures in patients with CrCl $>$ 60 mL/minute. If moderate renal impairment, CrCl of 30–59 mL/minute, discontinue apixaban 72 hours before procedure and 96 hours before high-risk endoscopic procedures in severe renal impaired patients (CrCl of 15–29 mL/minute).[20] In low bleeding risk procedures such as dental procedures (excluding multiple tooth extractions), cutaneous procedures (biopsy, superficial tumor excision), and low-risk cardiac procedures such as implantable devices and endovascular procedures, apixaban may be continued, as evident in the ARISTOTLE trial where approximately one-third (37.9%) did not interrupt anticoagulation treatment in the apixaban arm.[28]

Novel factor Xa inhibitors have a rapid onset of action in the blood stream as noted by pharmacokinetics with maximum concentration three to four hours after ingestion of apixaban. Preoperatively, patients should be assessed for risk of stroke and thrombosis while off anticoagulation for high bleeding risk procedures.

Edoxaban (Savaysa).

Mechanism of action. Edoxaban, known by the brand name Savaysa, reduces blood coagulation by directly inhibiting factor Xa, much like rivaroxaban and apixaban. In the simplest sense, all three of these drugs decrease thrombin generation, and in doing so, decrease the formation of thrombi, which produces a state that opposes coagulation. Edoxaban impacts multiple coagulation tests, namely, partial thromboplastin time and anti-Xa assay, which have both been shown to accurately indicate drug levels within the plasma.[17]

Pharmacokinetics. Edoxaban is administered orally, and it takes between one and two hours for it to reach peak plasma concentration. Edoxaban has a 107-L volume of distribution, is about 55% protein bound, and has a bioavailability of 62%. The half-life of edoxaban ranges from 10 to 14 hours, and in the plasma, it is most often found in the form of unchanged edoxaban. Edoxaban is a substrate of the P-glycoprotein transporter. About half of it is renally cleared, and when excreted via the urine, it is predominately done so in the form of unchanged drug.[29]

Indications, dosing, and drug interactions. Edoxaban is used to protect against stroke and systemic embolism in instances of nonvalvular atrial fibrillation. In such instances, the patient must have a CrCl of less than 95 mL/minute as it was noticed that edoxaban increases the risk of ischemic stroke when compared to warfarin. It is also indicated after a hip or knee

arthroplasty for the prevention of venous thrombotic events. Another crucial use of edoxaban is to treat DVT and PE in those who received a parenteral anticoagulant 5 to 10 days prior.[30] In the ENGAGE AF-TIMI trial, the rates of both stroke and embolism were lower in those given edoxaban compared to those given warfarin. More specifically, in patients given warfarin, the rate of systemic emboli was 1.50%, and in patients given high-dose or low-dose edoxaban, the rates of systemic emboli were 1.18% and 1.61%, respectively.[31]

Edoxaban, an oral medication that can be taken without food, is available in 15, 30, and 60 mg tablets. In patients with atrial fibrillation, a dose of 60 mg orally daily is recommended for stroke prophylaxis if CrCl is between 50 and 95 mL/minute. If the CrCl is between 15 and 50 mL/minute, dose is adjusted to 30 mg orally daily. For DVT or PE treatment following use of a parenteral anticoagulant, a dose of 60 mg orally daily is recommended in patients weighing greater than 60 kg, and one of 30 mg orally daily in those weighing less than 60 kg.[29] If the CrCl is between 15–50 mL/minute, dose is adjusted to 30 mg orally daily for both stroke prophylaxis with nonvalvular atrial fibrillation and DVT or PE treatment.

Edoxaban is minimally metabolized by hydrolysis, conjugation, and oxidation involving CYP3A4. It is also a substrate of P-glycoprotein. Edoxaban's main contraindication is with defibrotide. However, edoxaban is also listed as a Risk X with the following medications: anticoagulants (excluding acenocoumarol and warfarin), apixaban, dabigatran, omacetaxine, rifampin, rivaroxaban, urokinase, and vorapaxar. This means that edoxaban should not be used in conjunction with any of these medications. By decreasing serum concentration of edoxaban, the P-glycoprotein/ABCB1 inducers may also limit the distribution of the drug in the body. For instance, certain organ tissues and cells (the brain, T-lymphocytes, and testes) possess P-glycoprotein in larger amounts. These same areas will have comparatively less edoxaban in the presence of an inducer than will other areas. For this reason, P-glycoprotein inducers are categorized as Risk C and must be monitored closely when administered with edoxaban. Additionally, P-glycoprotein inhibitors cause the opposite effect and run the risk of high serum levels of edoxaban. Since this might produce too much anticoagulation, P-glycoprotein inhibitors are categorized as Risk D, which means that it is important to consider therapy modification. For example, in patients taking edoxaban for VTE, a dose reduction is recommended if the patient also takes a P-glycoprotein inhibitor. A dose adjustment is not recommended, however, in patients taking edoxaban for atrial fibrillation, even if they are also taking an inhibitor.[30]

Contraindications and side effects. It is recommended that dosage be adjusted in patients with mild hepatic impairment (Child-Pugh class A) and that the drug be avoided entirely in those with moderate-to-severe hepatic impairment (Child-Pugh classes B and C). According to the International Society on Thrombosis and Haemostasis, edoxaban and other oral anticoagulants, in general, are not recommended in those with a BMI of greater than 40 kg/m^2 or a weight of greater than 120 kg.[32] Guidelines exist for how to properly dose edoxaban in patients with renal impairment, taking into account both their CrCl and the reason for needing anticoagulation in the first place.

Even with these dose adjustments, as stated earlier, edoxaban should be avoided in those with active pathological bleeding, a Child-Pugh classification of B or C, a prior reaction to dabigatran, liver disease with coagulopathy, or a CrCl of less than 15 mL/minute or greater than 95 mL/minute. Additionally, since molecule size of these oral anticoagulants is small, they can pass through the placenta and must be avoided in pregnancy. Edoxaban in particular is pregnancy category C drug, along with dabigatran and rivaroxaban.[30]

As with most anticoagulants, including the new oral anticoagulants, the greatest risk is for bleeding, which makes sense given their fundamental mechanism of action. Thus, an obvious contraindication to edoxaban and other oral anticoagulants is active pathological bleeding.[33] Of particular concern is the possibility of an epidural or spinal hematoma that could result from taking edoxaban along with neuraxial anesthesia or during a spinal puncture, which could result in permanent paralysis.[30]

Despite this adverse effect, edoxaban has still been shown to be preferable to warfarin with regard to reducing major bleeding events. In one study, edoxaban was found to be just as effective as warfarin in preventing recurrent VTE in patients with acute PE or DVT. At the same time, those treated with edoxaban developed fewer bleeding complications, at a rate of 8.5% versus 10.3%.[34] Compared to warfarin, these new oral anticoagulants produce less intracranial bleeding than warfarin does. However, at the same time, they have been found to produce more gastric bleeding than warfarin. Other side effects of edoxaban include abnormal liver function tests (4.8%), rash (4.2%), anemia (1.7%), and general bleeding (9.4%).[29]

Perioperative management of patients on edoxaban. Very limited data exist in the literature regarding the perioperative risk of interrupting edoxaban use. Likely due to the recent FDA approval of edoxaban on January 8, 2015, and various black box warnings associated with the medications, it has not been widely integrated into general practice of clinicians. In the ENGAGE AF-TIMI 48 trial, comparing edoxaban and warfarin for stroke prevention in atrial fibrillation population, 3,116 patients had drug interruption (discontinued apixaban 4–10 days prior to procedure) and 4,077 patients continued apixaban (discontinuation of apixaban, 3 days or less prior to procedure). Analysis of the perioperative period did not show any statistical significance in both studied arms with similar outcomes in terms of stroke or systemic embolism, whether the drugs were discontinued or not.

Analysis of the ENGAGE AF-TIMI 48 trial evaluated patients for their increase in major bleeding episodes and death from all causes. Bleeding risk is increased if anticoagulation is not interrupted in the perioperative period, and such bleeding risk did not differ from forms of anticoagulation whether it is a

vitamin K antagonist or factor Xa inhibitor such as edoxaban.[35] Patients who were randomized to warfarin were further evaluated based on interruption and uninterruption, 11 events out of 1,041 patients and 34 events out of 1,405 were noted respectively. Patients were further split into 30 and 60 mg of edoxaban based on dose reductions due to renal function, and again evaluations of the interrupted and uninterrupted population were performed. Patients who received 30 mg of edoxaban had 12 out of 1,012 events in the interrupted arm and 35 out of 1,367 events in the uninterrupted arm. Edoxaban 60 mg exhibited similar results, 11 out of 1,063 events noted in the interrupted population and 47 out of 1,305 in the uninterrupted population.[35]

Based on the aforementioned clinical analysis of the ENGAGE AF-TIMI 48 trial, decisions whether to discontinue edoxaban should be closely weighted by factors such as patients' risk for thrombosis and bleeding risk during the procedure. In patients with increased risk of thromboembolism, bridging with shorter acting anticoagulants such as unfractionated heparin is recommended.[36]

In high bleeding risk procedures, edoxaban should be discontinued 72 hours prior. Edoxaban is recommended to be discontinued at least 24 hours prior to low bleeding risk procedures, irrespective of renal functional status.[20]

In the perioperative setting, the driving force that dictates whether to bridge anticoagulation is determined by patients' risk for thromboembolism and stroke. Atrial fibrillation risk of stroke is determined by the $CHADS_2VASc$ score, and risk of VTE is determined by timing of most recent VTE and inherited or acquired thrombophilias. In high-risk thromboembolic patients, bridging of edoxaban is recommended prior to procedure; however, due to the rapid onset of edoxaban, bridging postoperatively is usually not required.[36]

Summary and Future Directions

Management of patients on DOACs in the perioperative period is now an important know-how in the era of increasing number of patients on DOACs. It requires the assessment of thromboembolic event risk while off anticoagulation compared to the relative risk of bleeding if such drug is continued. DOACs may be successfully managed in the perioperative period with consideration given to the pharmacokinetics of the DOAC, renal function of patients, risk of bleeding with respective to the procedure or surgery, and thromboembolic risk of the patient.

The common pitfalls in this rapidly changing field of DOACs include improper timing of either stopping or restarting the medications periprocedure. This review serves as a concise resource that would aid a practicing clinician in making an informed decision. Additional large randomized, prospective studies are needed to further characterize the safety and management of newer DOACs in the perioperative period. Future research in the area of DOACs could also probably entail development of protocols for monitoring anticoagulation status and development of specific antidotes for reversal.

Author Contributions

Conceived and designed the review article: TS, EO, and MR. Analyzed the data: TS and EO. Wrote the first draft of the manuscript: TS and EO. Jointly developed the structure and arguments for the paper: TS, EO, VZ, MEC, VG, and MR. Contributed to the writing of the manuscript: TS, EO, VZ, MEC, and VG. Agreed with manuscript results and conclusions: TS, EO, VZ, MEC, VG, and MR. Made critical revisions and approved the final version: TS, VG, and MR. All the authors reviewed and approved the final manuscript.

REFERENCES

1. Riva N, Lip G. A new era for anticoagulation in atrial fibrillation. Which anticoagulant should we choose for long-term prevention of thromboembolic complications in patients with atrial fibrillation? *Pol Arch Med Wewn*. 2012;122:45–53.
2. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:326S–350S.
3. Tran H, Joseph J, Young L, et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. *Intern Med J*. 2014;44(6):525–536.
4. Turpie AGG, Kreutz R, Llau J, Norrving B, Haas S. Management consensus guidance for the use of rivaroxaban—an oral, direct factor Xa inhibitor. *Thromb Haemost*. 2012;108(5):876–886.
5. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. *Blood*. 2012;120(15):2954–2962.
6. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8(1):202–204.
7. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. *Circulation*. 2011;123(23):2736–2747.
8. Douketis JD. Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach. *Blood*. 2011;117(19):5044–5049.
9. Sherwood MW, Douketis JD, Patel MR, et al. Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation*. 2014;129(18):1850–1859.
10. Zehnder JL. Drugs used in disorders of coagulation. In: Katzung BG, Trevor AJ, eds. *Basic & Clinical Pharmacology, 13e*. NewYork, NY: McGraw-Hill; 2015. Available at: http://accessmedicine.mhmedical.com.arktos.nyit.edu/content.aspx?bookid=1193&Sectionid=69108955. Accessed August 31, 2016.
11. Dabigatran: drug information. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate; 2016.
12. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate. *Clin Pharmacokinet*. 2010;49(4):259–268.
13. PRADAXA® (dabigatran etexilate mesylate). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2010, 2012, 2013.
14. Stangier J, Eriksson BI, Dahl OE, et al. Pharmacokinetic profile of the oral direct thrombin inhibitor dabigatran etexilate in healthy volunteers and patients undergoing total hip replacement. *J Clin Pharmacol*. 2005;45(5):555–565.
15. Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511–520.
16. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369(13):1206–1214.
17. Samama M, Contant G, Spiro TE, et al. Laboratory assessment of rivaroxaban: a review. *Thromb J*. 2013;11(1):11.
18. Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the randomized evaluation of long-term anticoagulation therapy (RE-LY) randomized trial. *Circulation*. 2012;126(3):343–348.
19. Schulman S, Carrier M, Lee AYY, et al. Perioperative management of dabigatran clinical perspective. *Circulation*. 2015;132(3):167–173.
20. Acosta RD, Abraham NS, Chandrasekhara V, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc*. 2016;83(1):3–16.
21. Rivaroxaban: drug information. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate; 2016.

22. Xarelto (rivaroxaban). Titusville, NJ: Janssen Pharmaceuticals, Inc; 2011, 2016.
23. Eikelboom J, Sobieraj-Teague M, Ginsberg JS. Chapter 261. Anticoagulant therapy. In: McKean SC, Ross JJ, Dressler DD, Brotman DJ, Ginsberg JS, eds. *Principles and Practice of Hospital Medicine*. New York, NY: McGraw-Hill; 2012. Available at: http://accessmedicine.mhmedical.com.arktos.nyit.edu/content.aspx?bookid=496&Sectionid=41304257. Accessed September 11, 2016.
24. EINSTEIN Investigators, Bauersachs R, Berkowitz S, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499–2510.
25. Apixaban: drug information. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate; 2016.
26. ELIQUIS (apixaban). Princeton, NJ; New York, NY: Bristol-Myers Squibb Company & Pfizer Inc; 2012, 2016.
27. Trevor AJ, Katzung BG, Kruidering-Hall M. Drugs used in coagulation disorders. In: Trevor AJ, Katzung BG, Kruidering-Hall M, eds. *Katzung & Trevor's Pharmacology: Examination & Board Review, 11e*. New York, NY: McGraw-Hill; 2015. Available at: http://accessmedicine.mhmedical.com.arktos.nyit.edu/content.aspx?bookid=1568&Sectionid=9570369. Accessed September 11, 2016.
28. Garcia D, Alexander JH, Wallentin L, et al. Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing procedures. *Blood*. 2014;124(25):3692–3698.
29. SAVAYSA (edoxaban). Parsippany, NJ: Daiichi Sankyo, Inc; 2015.
30. Edoxaban: drug information. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate; 2016.
31. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093–2104.
32. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14(6):1308–1313.
33. Weitz JI. Antiplatelet, anticoagulant, and fibrinolytic drugs. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, 19e*. New York, NY: McGraw-Hill; 2015. Available at: http://accessmedicine.mhmedical.com.arktos.nyit.edu/content.aspx?bookid=1130&Sectionid=79732627. Accessed September 01, 2016.
34. Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406–1415.
35. Douketis J, Weitz J, Murphy S, et al. Perioperative adverse outcomes in patients with atrial fibrillation taking edoxaban or warfarin: analysis of the ENGAGE AF-TIMI 48 TRIAL. *J Am Coll Cardiol*. 2015;65(10_S). A2092.
36. Zalpour A, Oo TH. Update on edoxaban for the prevention and treatment of thromboembolism: clinical applications based on current evidence. *Adv Hematol*. 2015;2015:920361, 19.