Review Article

Direct Oral Anticoagulants: How Do These Drugs Work, How to Monitor, and What Is Their Role in Orthopaedic Surgery

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ABSTRACT

Postoperative venous thromboembolism is a major adverse event associated with orthopaedic surgery. With the addition of perioperative anticoagulation and antiplatelet therapy, the rates of symptomatic venous thromboembolism have dropped to 1% to 3%, and as such, practicing orthopaedic surgeons must be familiar with these medications, including aspirin, heparin, or warfarin, and the use of direct oral anticoagulants (DOACs). DOACs are increasingly being prescribed due to their predictable pharmacokinetics and increased convenience, as they do not require routine monitoring, and 1% to 2% of the general population is currently anticoagulated. Although the introduction of DOACs has yielded additional treatment options, this has also led to confusion and uncertainty regarding treatment, specialized testing, and when and what reversal agents are appropriate. This article provides a basic overview of DOAC medications, their suggested use in the perioperative setting, effects on laboratory testing, and consideration for when and how to use reversal agents in orthopaedic patients.

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A host of factors lead to a prothrombotic state in orthopaedic surgery (OS), including utilization of operational tourniquets, localized vascular injury during surgical manipulation, use of prothrombotic surgical materials including cement, and subsequent immobility during recovery.[1,2] These factors have historically led to rates of VTE and fatal PE, approaching 50% and up to 20%, respectively.[3] With implementation of anticoagulant therapy, modification of surgical techniques, and earlier mobilization of patients, the incidence of VTE/fatal PE reported with OS has progressively declined to around 1% to 3%.[1,2,4]

Oral vitamin K antagonists (VKAs) such as warfarin (Coumadin) have historically served as the primary oral anticoagulant in this setting, with subsequent adoption of heparin for inpatients. Although utilization of VKAs led to a substantial drop in thromboembolic events associated with OS, these anticoagulants have inherent disadvantages such as drug interactions,

Table 1. Basic Pharmacokinetics of Direct Oral Anticogulants

Pharmacokinetic Parameter	Dabigatran (Brand Name Pradaxa)	Rivaroxaban (Brand Name Xarelto)	Apixaban (Brand Name Eliquis)	Edoxaban (Brand Name Savaysa)
Mechanism of action	Direct thrombin inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
FDA approval	Total hip arthroplasty	Total hip arthroplasty and total knee arthroplasty	Total hip arthroplasty and total knee arthroplasty	—
Half-life (hr)	12-17 in healthy adults 14-18 in elderly	5-9 in healthy adults 11-13 in elderly	12	10-14
Time to peak (hr)	1-2	2-4	3-4	1-2
Metabolism (approximate)	80% renal/20% hepatic	35% renal/65% hepatic	25% renal/75% hepatic	50% renal/50% hepatic
Dosing	110 mg orally first day and then 220 mg once daily	Hip arthroplasty: 10 mg once daily for 35 d; knee arthroplasty: 10 mg once daily for 12 d	2.5 mg twice daily	—
Renal dosing	Use not recommended in patients with reduced renal function	Use not recommended in patients with reduced renal function	2.5 mg twice daily	—
Hepatic dosing	No dose adjustment in patients with moderate liver disease	Use not recommended in patients with moderate to severe liver disease	Not recommended in patients with moderate to severe liver disease	—
Use in extremes of weight	Not recommended	Yes (dose adjustment not well established)	Yes (dose adjustment not well established)	Not recommended

All data were obtained from package inserts, Lexicomp database entries, Covert et al, Martin et al, and Qamar et al.[6,14,16,18,19]
If using in patients with reduced creatinine clearance, moderate to severe liver disease, or extremes of body weight, routine monitoring and consultation with the hospital pharmacy should be considered.

dietary restrictions, differential drug metabolism among patients, and the need for routine laboratory monitoring.

After FDA approval, direct oral anticoagulants (DOACs) have become the predominant anticoagulant used in the outpatient setting and are increasingly being used in OS patients in the postoperative setting.[5] Among the factors driving their increasing use are their predictable pharmacokinetic profile, eliminating the need for routine monitoring, and fewer major bleeding events. After FDA approval of dabigatran (Pradaxa), the drugs rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) have all received approval, with most of these currently being used as FDA-approved anticoagulation for total hip arthroplasty or total knee arthroplasty.[6,7]

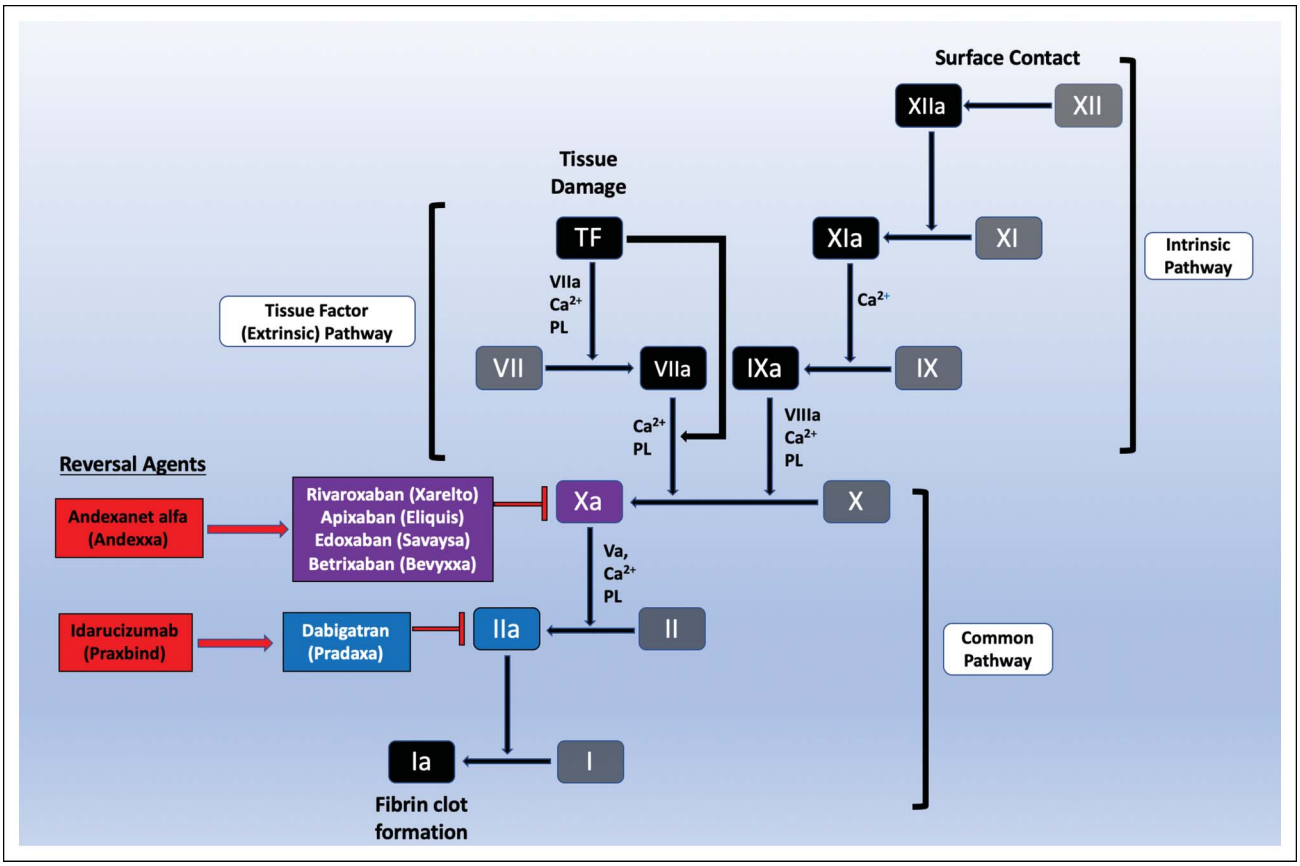
Understanding of the changing anticoagulation landscape is important for practicing orthopaedic physicians.[3,4] In addition to being familiar with indications for their use, DOAC medications present specific challenges in regard to appropriate laboratory testing, bridging requirements, and reversal modalities, which are detailed herein.

DOACs: Benefits and Mechanism of Action

At present, there are two major categories of DOACs: dabigatran (Pradaxa), a thrombin inhibitor, and anti-Xa inhibitors including rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) (Table 1). In vivo, factor Xa interacts with factor V to form the prothrombinase complex, which converts prothrombin to thrombin, and in turn, thrombin converts fibrinogen to fibrin (Figure 1).[8] As such, both drug classes ultimately block fibrin production via the common pathway and have variable effects on several clot-based laboratory tests (Figure 1).

Although VKAs have inherent limitations that include the need for laboratory monitoring, dietary restrictions, differential metabolism, and a narrow therapeutic range, multiple issues arise in patients receiving DOACs.[9] As 1% to 2% of patients are on DOACs chronically, it is unfortunate that strategies for DOAC management in patients undergoing surgery or requiring reversal for major hemorrhage (incidence of 2% to 3.5%) are still not well established.[10-13] Moreover, although DOACs demonstrate predictable pharmacokinetics in most

Figure 1



Clotting cascade with location of action for common oral direct Xa and IIa inhibitors. Reversal agents are shown in red boxes.

patients, dosing adjustments may be required, or drugs may be contraindicated in the context of renal dysfunction, moderate to severe liver disease, or patients at extremes of body weight. Finally, in patients with suspected failure of medications (deep vein thrombosis/-pulmonary embolism development on therapy), DOAC interference with thrombophilia testing must be considered when evaluating patients with breakthrough venous thromboembolism (VTE). Ultimately, increased familiarity with pharmacokinetic characteristics of these agents and their effect on laboratory testing will assist with perioperative management both with anticoagulation of surgical patients for VTE prevention and the surgical management of patients on chronic DOAC therapy.

Types of DOAC

Dabigatran

Dabigatran (Pradaxa) inhibits the proteolytic activity of free thrombin and thrombin bound to fibrin (Table 1). It is ingested as a prodrug and requires conversion via the liver for activity.[6,8,14] Currently, dabigatran is FDA approved for VTE prophylaxis in total hip arthroplasty, although the literature has also demonstrated its utility in an off-label context for prophylaxis after total knee arthroplasty.[14] It should be noted that a large proportion of the drug undergoes renal clearance (80% renal and 20% biliary), and its use is generally discouraged with CrCl <30 mL/min due to the reportedly higher incidence of major bleeding events in this patient population.[15] Moreover, the use of dabigatran is frequently discouraged in patients at extremes of body weight (body mass index [BMI] >35 kg/m^2 or weight <50 kg).[16,17]

Factor Xa Inhibitors

The factor Xa inhibitor drugs inhibit both free and bound factor Xa (Table 1). Although not all agents are in routine use for orthopaedic surgery VTE prophylaxis, their indications continue to expand.

Rivaroxaban

Rivaroxaban (Xarelto) has high oral bioavailability (80%) and a variable half-life (Table 1).[6,8,14] Rivaroxaban is

FDA approved for VTE prophylaxis after total hip arthroplasty and total knee arthroplasty.[14] Rivaroxaban undergoes renal and hepatic excretion (35% renal and 65% biliary), and care should be taken to avoid this medication in patients with renal impairment or moderate to severe liver disease.[6,18] Evidence has demonstrated that rivaroxaban is similarly efficacious in patients with obesity (BMI >35 kg/m^2).[19]

Apixaban

Apixaban (Eliquis) has 50% oral bioavailability and predictable drug metabolism (Table 1).[6,8,14] FDA-approved orthopaedic indications for apixaban include total hip arthroplasty and total knee arthroplasty. Among DOACs, apixaban has the lowest degree of renal excretion (25% renal and 75% biliary). Accordingly, apixaban is preferentially used in patients with chronic kidney disease, although appropriate renal dosing and routine monitoring are recommended.[20] Anticoagulation with apixaban is discouraged in patients with CrCl <15 mL/min[6] Because most drug metabolism occurs within the liver (75% biliary), this medication should be used with caution in patients with moderate liver disease (Child-Pugh score 7 to 9) and should be avoided in patients with severe liver disease (Child-Pugh score 10 to 15).[18] Data regarding the use of apixaban in patients with obesity are limited; although it seems to be safe, and although dose adjustment may be considered, no formal recommendations have been made.[16,19]

Edoxaban

Edoxaban (Savaysa) has ~60% oral bioavailability and predictable drug metabolism (Table 1).[6,8,14] Although multiple trials have been performed, at present, no FDA-approved orthopaedic indications exist, but it is currently in use for VTE prophylaxis in patients with atrial fibrillation and treatment of DVT/PE.[6] Approximately 50% of edoxaban undergoes renal clearance, with the remaining 50% cleared via the biliary tract. Edoxaban has not been studied extensively in patients at extremes of body weight, and therefore, its use is not recommended in patients with a BMI of >35 kg/m^2 or weight <50 kg.[16]

Laboratory Testing

While routine monitoring of DOACs is not required, the laboratory evaluation DOAC drugs may be employed to guide therapy in OS patients (Table 2). Specifically, the presence of drug effect should be determined in patients undergoing invasive procedures or those with major hemorrhage. Conversely, in patients with VTE on therapy, testing can help distinguish breakthrough clotting vs medication nonadherence. Testing is also essential in cases of suspected overdose or decreased medication clearance, specifically in patients with renal disease. Currently, the thrombin time is the preferred test for identifying drug effect with dabigatran, and chromogenic factor Xa assays are preferred for Xa inhibitors; however, a broader menu of testing is available, and DOAC effects on coagulation tests are reviewed herein.

Partial Thromboplastin Time

The partial thromboplastin time (PTT) measures the intrinsic pathway (factors VIII, IX, XI, and XII) via contact activation and the common pathway factors (factors I, II, V, and X).[8] As the PTT assesses the common pathway, it is to be anticipated that DOAC medications will prolong this value, although this may not always be the case. Unfortunately, the PPT prolongation associated with DOAC medications, both dabigatran and Xa inhibitors, is variable from reagent to reagent.[21] PTT may demonstrate the presence of the drug but should not be used for monitoring, and each lab should determine assay sensitivity to these drugs.

Prothrombin Time and International Normalization Ratio

The prothrombin time (PT) measures the extrinsic (factor VII) and common (factors I, II, V, and X) coagulation pathways and is standardized between labs with the international normalization ratio for VKA monitoring. Anti-Xa inhibitors should prolong the PT, and this is most pronounced in patients on rivaroxaban and edoxaban.[22] Again, a prolonged PT can help rule in drug effect, but this prolongation is reagent specific and cannot be reliably used for monitoring; likewise, international normalization ratio elevations may occur but should not be used to make specific clinical decisions.[8,22] Dabigatran should prolong the PT, but there is variability between reagents and testing platforms.[21] Once more, the absence of PT prolongation, as with PTT, does not rule out the presence of drug, and futher labs should determine sensitivity to DOAC medications.

Thrombin Time

The thrombin time (TT) measures the time required for fibrinogen to be converted to fibrin when thrombin is present.[8,21] Consequently, TT will be prolonged if fibrin production is inhibited by a drug, dysfibrinogenemia, or low fibrinogen.[8] Anticoagulants that prolong TT include dabigatran, argatroban, bivalirudin, and unfractionated heparin (UFH). The TT is a sensitive assay to dabigatran drug effects, even below on therapy range, and a diluted

Table 2. Coagulation Laboratory Tests and effects of Direct Oral Anticoagulants

Assay	Direct Thrombin Inhibitors (Dabigatran)	Direct Xa Inhibitors (Rivaroxaban, Apixaban, and Edoxaban)
aPTT	Prolonged	Prolonged
PT/INR	Prolonged	Prolonged
TT	Prolonged	No effect
Fibrinogen (Clauss)	No effect or low	No effect
AT	IIa based: overestimated, Xa based: no effect	IIa based: no effect, Xa based: overestimated
PC activity (clot based)	Overestimated	Overestimated
PS activity (clot based)	Overestimated	Overestimated
aPCR	False negative	False negative
LA testing	Possible to misclassify as LA	Possible to misclassify as LA

PT/INR = prothrombin time/international normalization ratio, TT = thrombin time
Adapted from (Adcock) Funk.[36]

thrombin time can be useful for accurately measuring drug levels.[22] TT is unaffected by anti-Xa DOAC medications.[21]

Anti-Xa Assays (Chromogenic)

Chromogenic anti-Xa assays have been used to monitor the drug effects of UFH, low-molecular-weight heparin (LMWH), and fondaparinux. These chromogenic assays measure factor Xa's ability to cleave a chromogenic substance in the presence of patient plasma, in contrast to clot-based Xa activity assays. It should be noted that DOAC calibrators are available, but these are non-FDA approved and consequently must be validated as a laboratory-developed test; thus, use of these tests in most institutions is not readily available.[23] Alternatively, anti-Xa assays calibrated for UFH/LMWH have been shown to correspond with drug effect and can be obtained quickly, with qualitative values rapidly available to guide intraoperative practice.[23] However, each lab must determine sensitivity to DOACs with their specific chromogenic assay before use in a clinical setting. These assays are not affected by dabigatran because the drug has no anti-Xa activity.

Fibrinogen

Functional fibrinogen assays will demonstrate falsely low fibrinogen levels in patients on dabigatran.[21] Immunoassays such as ELISA will be unaffected by dabigatran use. Anti-Xa DOAC medications will not affect the results of either methodology.

Viscoelastic Testing

Rotational thromboelastography (TEM International, Munich, Germany), thromboelastography (Haemonetics, Braintree, MA), and more recently Sonic Estimation of Elasticity via Resonance Sonorheometry (Hemosonics Charlottesville, VA) are capable of demonstrating clot formation in real time.[23] Unfortunately, viscoelastic testing has shown variable results in predicting DOAC levels based on clot formation outside of an anticipated prolongation, and these assays are relatively insensitive to DOAC trough levels.[24] Surgeons should be aware of these implications on interoperative testing and may consider relying on thrombin times for patients on dabigatran or anti-Xa testing for other DOAC medications if rapidly available, as viscoelastic testing and other point-of-care tests such as the activated clotting time are unreliable in this setting.

Additional Laboratory Assessment

In general, patients receiving DOACs should undergo laboratory evaluation of renal and liver function on an annual basis, based on the current literature and personal experience.[25] Likewise, in patients with multiple comorbidities or conditions that affect renal or hepatic function, it is recommended that laboratory evaluation occurs every 3 to 6 months for patients with renal disease and every 6 months for those with hepatic impairment.[25]

Perioperative Management

Anticoagulation in Orthopaedic Patients

Anticoagulant use in the postsurgical period is associated with an increase in hemorrhagic adverse effects.[2] Therefore, it is important to recognize patients at high risk for clots either due to the nature of the surgery or specific comorbidities. Surgeries at moderate to high risk for

postoperative VTE include total hip or knee arthroplasty, hip fracture surgery, and spinal cord injury. In contrast, low- to moderate-risk procedures include knee arthroscopy, distal lower leg injuries, elective spine surgery, and upper extremity surgery.[1] Risk factors for clotting include age, obesity, smoking, oral contraceptive use, previous VTE, malignancy, and immobility, among others.[1,2] Unfortunately, large-scale randomized controlled trials assessing models to predict clotting or bleeding in OS patients do not exist, and further studies are warranted.[2]

Because most clots occur after discharge, the ability to prevent VTE in the outpatient setting is critical, with some anticoagulation regimens lasting as long as 35 days.[2] There are numerous postoperative anticoagulation guidelines, with most recommending LMWH over UFH and more recent guidelines recommending DOAC medications over VKAs (warfarin).[1,2,26] In general, mechanical compression devices can be used postoperatively, with anticoagulation reserved for high-risk procedures or patients undergoing moderate-risk surgery with multiple risk factors for VTE. Aspirin has been compared with anticoagulation (heparin or VKAs), demonstrating no significant difference in the incidence of clotting or bleeding, although direct comparisons to DOACs are ongoing.[2] Moreover, although aspirin represents an attractive monotherapy given the price and ease of dosing, randomized controlled trials are still needed because most existing studies are retrospective or low quality.[2,26] Flevas et al[1] offer a more extensive review of dosing guidelines, combination therapy, the timing of anticoagulation, and a comprehensive listing of societal recommendations. Similarly, the recent International Consensus Meeting guidelines for VTE prophylaxis and management are a useful resource.[27]

Although there are a number of benefits afforded by DOACs, robust literature characterizing their use for VTE prophylaxis in OS does not exist. Although DOAC use in elective OS patients undergoing presurgical evaluation seems evidence based, data supporting use in trauma or those with severe chronic illness, such as malignancy, are limited. Meta-analyses suggest that DOACs are better or equally as effective when used for VTE prophylaxis with similar rates of clinically significant bleeding when compared with conventional anticoagulants such as LMWH.[28,29] Moreover, current literature has demonstrated no difference between DOAC and aspirin after OS.[30] Collectively, the existing data suggest that DOACs do have a role in VTE prophylaxis in OS patients without significant risk factors undergoing elective surgery. However, at this time, evidence supporting the use of DOACs in orthopaedic trauma or those with malignancy is limited.

Perioperative Anticoagulant Management for Elective Procedures

A significant proportion of patients, 1% to 2% of the general population, is on anticoagulant medications, specifically older individuals who would be more likely to undergo hip or knee arthroplasty; likely management of patients on DOAC medications will not only be encountered but become more common in the coming years.[13] The recently published Perioperative Use for Surgery Evaluation cohort study evaluated discontinuation of DOAC in surgical patients without heparin bridging.[31] The study was conducted over 4 years and included 3,007 patients receiving DOACs (apixaban, dabigatran, or rivaroxaban) for atrial fibrillation.[31] After discontinuation of anticoagulation 1 day before and reinitiating anticoagulation 1 day after low-bleeding risk surgeries and ~2 days for high-bleeding risk procedures, investigators observed low rates of major bleeding ~2% and stroke <1%.[30] Residual DOAC levels were <50 ng/mL in 95.1% of the low-risk group at the time of surgery and 98.8% in the high-risk group, suggesting minimal residual drug effect for most of these procedures.[31] It should be noted that the Perioperative Use for Surgery Evaluation study did not specifically focus on OS patients; thus, additional studies evaluating this patient population are warranted; however, these findings do support routine discontinuation of DOAC in AF patients for a number of procedures.[31]

Emergent/Invasive Interventions

Bleeding is an anticipated complication/adverse event inherent to anticoagulant therapy, with devastating intracranial hemorrhage or intractable GI bleeding being of the utmost concern. Recent literature has shown that with increased anticoagulation use in the orthopaedic surgery population, the rates of clinically significant bleeding are 3.44%.[4] Therefore, in addition to a more tailored approach when selecting patients who should be treated with anticoagulation, an understanding of the therapeutic management of DOAC-associated bleeding is necessary, especially given the mortality rate of 17.7% reported with DOAC-associated bleeding.[13] Currently, the International Society on Thrombosis and Haemostasis Subcommittee on Control of Anticoagulation recommends only using reversal agents in the setting of clinically significant bleeding or the need for emergent surgery with a significant amount of anticipated bleeding.[32] Standard coagulation labs should be assessed before

pharmaceutical intervention, and reversal agents should not be used if these parameters do not show drug effect, as these agents have been associated with thrombotic events. As many DOAC medications have short half-lives, the renal and hepatic function should be assessed, if time permits, to help contextualize drug levels in relation to the last dose. Optimization of other clotting parameters with platelets or fibrinogen support may also be considered. Finally, anticoagulation should be resumed for patients at an appropriate time after surgical intervention. Cuker et al[12] published a guidance document from the Anticoagulation Forum for DOAC reversal agents, which is a useful resource. Specific reversal agents are detailed below.

Reversal Agents

When evaluating the safety of DOAC reversal, it is important to underscore that patients anticoagulated with these agents inherently possess prothrombotic risk factors. Consequently, it is often difficult to attribute TEs observed after the utilization of reversal agents to the agent or to prolonged cessation of anticoagulation. Accordingly, timely reinitiation of anticoagulation after reversal is essential to reducing the incidence of TEs. Finally, older medications used for VKA reversal such as IV vitamin K or 4-factor prothrombin complex concentrate (4F-PCC) are readily available and less expensive than novel reversal agents but are not specifically designed to correct DOAC-associated bleeding. Care should be given when considering newer DOAC-specific agents because DOAC reversal is, as of yet, incompletely characterized in the medical literature.

Dabigatran-Idarucizumab

Idarucizumab (brand name Praxbind) is a humanized monoclonal antibody fragment with a high affinity for dabigatran and its metabolites, ultimately impeding dabigatran's inhibition of thrombin.[6,14] After infusion, idarucizumab has a rapid onset of action and relatively short half-life of approximately 47 minutes, with much of the drug undergoing renal clearance within 18 hours. The initial FDA approval of the drug was in 2015 with the Reversal Effects of Idarucizumab on Active Dabigatran study showing rapid improvement in bleeding with a median time to hemostasis of 2.5 hours in patients with active bleeds and 1.6 hours in patients undergoing invasive surgery.[6,12,33,34] In regard to safety, of the 301 patients with active bleeding and the 202 patients with reversal for surgery, the overall rates of thrombosis at 30 days were similar Group A4.8% (14/301) and Group B 5.0% (10/202). The patients with thrombosis in Group A and Group respectively had 79% (11/14) and 80% (8/10) of these TEEs occurring within 14 days of infusion.[12,33] Although the drug is rapidly cleared, it should be noted that in patients at high risk for VTE, discontinuation of anticoagulation or reversal of anticoagulation poses a thrombotic risk. In addition, at centers where idarucizumab is unavailable, PCC may be used. Finally, given the sensitivity of TT to dabigatran drug effect, we do not recommend using reversal agents in the context of a TT that falls within the normal reference range.

Anti-Xa–PCC

Current evidence suggests that PCC is the optimal reversal agent for anti–Xa-associated bleeding with lower rates of thrombosis (4.3% vs 10.7%) and mortality (17.4% vs 18.9%), with similar rates of achievement of hemostasis (80.1% vs 80.7%). Given the sensitivity of the heparin anti-Xa assay to the presence of factor Xa Inhibitor drug effect, we do not recommend utilization of reversal agents when the anti-Xa value falls under the reference range (0.5 to 1 IU/mL at our institution).

Anti-Xa–Coagulation Factor Xa (Recombinant), Inactivated-zhzo

Coagulation factor Xa (recombinant), inactivated-zhzo (brand name Andexxa) binds Xa inhibitors with high affinity and also binds and inhibits tissue factor pathway inhibitor.[6,12] This recombinant factor Xa is inactive as a clotting factor, acting as a decoy protein to reverse the effects of anti-Xa DOACs.[6,12] Unfortunately, the clinical trial for this medication had a 10% 30-day embolic event rate.[35] As such, despite receiving FDA approval, it carries a black box warning for thrombotic events, and additional studies are being conducted to further assess the safety of this medication.[6,12,35]

There was some controversy surrounding the Andexxa trial because there were concerns about the prothrombotic nature of the drug binding to tissue pathway factor inhibitor, the price point of the drug, and the trial design (single arm/no comparator).[35] An additional issue is the rebound effect after discontinuation of the infusion, which would possibly be encountered during a prolonged surgical procedure, given the drug's short half-life and apparent reversal activity of 2 to 4 hours with bolus dosing. The study enrollment criteria required an apixaban/rivaroxaban concentration >75 ng per milliliter.[35] Consequently, a significant proportion of patients with DOAC-

associated bleeding (28% 98/352) did not qualify for study inclusion.[35] Moreover, given the lack of ability to assess drug concentrations at most hospitals and the relatively short half-lives of DOAC medications, a significant proportion of patients excluded by the study may be receiving a drug that we have no data for. Therefore the reservations that many institutions have including this agent on their formulary can be understood.

Conclusion

DOAC medications will be increasingly prescribed for OS patients, and practitioners should be familiar with managing patients on these therapies. Although, generally, monitoring is not required, testing can be important in patients with reduced creatinine clearance, extreme weight, and bleeding or clotting while on therapy and in those requiring emergent surgery. Because rates of clinically significant bleeding remain high in OS patients on thromboprophylaxis, assessing each patient's specific needs and tailoring anticoagulation regimens will be required and should be a focus of further investigation.[1,2] Currently, care and attention and a multidisciplinary approach should be used whenever questions arise in OS patients on DOAC therapy.

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