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Anticoagulants and Surgery
So Many Agents, So Many Taking Them

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Keywords

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• Anticoagulation reversal • Direct oral anticoagulant (DOAC)
• Idarucizumab (Praxbind) • Novel oral anticoagulant (NOAC) • Andexxa

Key points

- The increasing number of direct oral anticoagulants available and the increasing frequency of their use makes perioperative anticoagulation management a great challenge.
- Strategies to determine the appropriate perioperative anticoagulation management rely on estimated thromboembolic risk versus bleeding risk using risk calculators, clinical experience, and basic understanding of the pharmacokinetics of the oral anticoagulant.
- Food and Drug Administration-approved reversal agents are available for dabigatran, rivaroxaban, and apixaban; however, there are few data to evaluate their efficacy and appropriate use, and they remain costly and of limited availability.
- There is a need for further studies to help standardize perioperative anticoagulation management that can still be tailored to meet individual patients' needs.

INTRODUCTION

The perioperative management of anticoagulation among patients undergoing surgical procedures has always been a challenge; surgeons need to balance the benefit of protection from thromboembolic events to the risk of bleeding during

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the perioperative period. This decision is not always easy and the increasing number of anticoagulation agents further complicates the perioperative decision if and when to interrupt therapy. Although vitamin K antagonists (VKA) have been the mainstay of anticoagulation therapy for decades, the relatively recent Food and Drug Administration (FDA) approval of several new direct oral anticoagulant (DOAC) agents has changed the landscape of anticoagulation therapy. DOACs are often preferred owing to their fixed dosing, decreased drug and food interactions, and lack of monitoring requirements. The 2014 American Heart Association/American College of Cardiology guidelines for the management of nonvalvular atrial fibrillation recommend DOACs as an alternative to warfarin, with several studies showing a reduced risk of intracranial hemorrhage with DOACs when compared with warfarin [1]. The 2016 American College of Chest Physicians guidelines favor DOACs over VKAs as a first-line therapy for venous thromboembolism (VTE) management in patients who do not have cancer [2]. This recommendation has resulted in a rapid increase in clinical use of DOACs, making encounter of these patients by surgeons increasingly more common. To further complicate the matter, newly FDA-approved reversal agents also exist for several of the DOACs, without sufficient data to evaluate their use in the perioperative setting. This article summarizes the FDA-approved DOACs and their reversal agents, and discusses strategies to determine the appropriate management of anticoagulation in the perioperative period to minimize both the thromboembolic and bleeding risks for patients undergoing surgical interventions.

PERIOPERATIVE ANTICOAGULATION MANAGEMENT

The management of anticoagulation in the perioperative setting requires an evaluation of the thromboembolic risk associated with interrupting anticoagulation therapy, the relative risk of bleeding associated with continuation of anticoagulation, the need for bridging therapy, and the specific anticoagulant agent itself.

Evaluation of thromboembolic risk

The most common indications for anticoagulation therapy include

- Atrial fibrillation,
- Recent VTE, and
- Prosthetic heart valves.

The CHA_2DS_2-VASc score is a validated risk stratification tool used to predict the risk of stroke and thromboembolism (TE) in a nonanticoagulated patient with nonvalvular atrial fibrillation (Table 1). Individuals can be stratified into low, moderate, or high thrombotic risk (Table 2) [3]. The degree of thrombotic risk can then be used to help determine the need for continuation of anticoagulation in the acute perioperative setting and whether or not the patient needs to be bridged with an unfractionated heparin (UFH) infusion preoperatively or postoperatively. A score of 0 is considered to be low risk for TE, a score of 1 is intermediate risk (0.6% at 1 year), and greater than 1 is high

Table 1
Thromboembolic risk stratification during anticoagulation interruption

Risk level	Atrial fibrillation	VTE	Mechanical heart valve
High	CHA_2DS_2-VASc score $\geq$2 Recent ischemic stroke or transient ischemic attack within 3 mo Rheumatic valvular heart disease	Recent VTE within 3 mo Severe thrombophilia (protein C/S deficiency, antiphospholipid antibodies, etc)	Any mitral valve prosthesis Recent stroke or TIA within 6 mo
Moderate	CHA_2DS_2-VASc Score of 1	VTE within 3–12 mo Nonsevere thrombophilia (eg, heterozygous Factor V Leiden) Recurrent VTE Active malignancy (treated within 6 mo or palliative)	Bileaflet aortic valve prosthesis with one or more: Atrial fibrillation, prior stroke or TIA, hypertension, diabetes, CHF, or age >75
Low	CHA_2DS_2-VASc score of 0	VTE $\geq$12 mo ago with no other risk factors	Bileaflet aortic valve prosthesis without atrial fibrillation or other risk factors

Abbreviations: CHF, congestive heart failure; TIA, transient ischemic attack.
Adapted from Douketis, J.D., Spyropoulos, A.C., Spencer, F.A., et al. Perioperative management of antithrombotic therapy. CHEST 2012;141(2):p. e326S–e350S; with permission.

risk (3% at 1 year) [4]. It is important to note that the CHA_2DS_2-VASc score has not been prospectively validated in the perioperative setting.

Up to 25% of patients undergoing abdominal surgery will develop deep vein thrombosis within 6 weeks of discharge [5]. Patients with a VTE within the

Table 2
CHA_2DS_2-VASc score calculator

Criterion	Value	Points
CHF	Yes	+1
Hypertension therapy	Yes	+1
Age	<65 years old	+0
	65–74 years old	+1
	$\geq$75 years old	+2
Diabetes history	Yes	+1
Stroke/TIA/VTE history	Yes	+2
Vascular disease history	Yes	+1
Sex	Male	+0
	Female	+1

Abbreviations: CHF, congestive heart failure; TIA, transient ischemic attack.
Data from Lip, G.Y., Vieuwlaat, R., Pisters, R., et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):p. 263–72.

preceding 3 months or with a history of VTE owing to a severe inherited thrombophilia are at high risk of a recurrent thromboembolic event in the perioperative setting if taken off therapeutic anticoagulation. Patients with a VTE within 3 to 12 months before surgery or who have an active malignancy are at moderate risk of VTE, and those with a history of VTE more than 12 months before surgery are at low risk of VTE perioperatively [3].

Patients with prosthetic valves are considered high risk for TE events. In general, bioprosthetic valves carry a lower TE risk compared with mechanical valves. It is not uncommon for patients with a bioprosthetic aortic valve to be on antiplatelet agents only, particularly those without atrial fibrillation. The TE risk is higher with mitral valve prostheses than with aortic valve prostheses; thus, patients with mechanical mitral valves should discontinue anticoagulation only for brief intervals during the perioperative period [3].

Estimating bleeding risk

The International Society on Thrombosis and Hemostasis for surgical studies defines major bleeding as bleeding that is fatal, involves a critical organ, requires surgery to correct, has a decrease in hemoglobin of 2 g/dL or more, or requires a transfusion of 2 or more units of packed red blood cells [5]. The consequences of bleeding complications depend on the nature of the surgical intervention being performed, as well as individual patient factors that may contribute to an increased volume of blood loss. Patients scheduled for eye procedures, neurosurgical or spine interventions, and those requiring neuraxial anesthesia are considered to be at high bleeding risk and should have all types of anticoagulation agents wear off completely before the planned procedure. In these situations, anticoagulants are restarted when the bleeding risk is minimal, usually several days after surgery. In addition, procedures that have a 2-day risk of major bleeding of 2% to 4%, such as vascular surgery, general surgery, prostatic resections, and polypectomies, are also considered high risk. Low risk of bleeding procedures have an estimated 2-day risk of major bleeding of 0% to 2%, such as abdominal hernia repair, axillary node dissection, and cholecystectomy, endoscopy [6].

In general, patients with a high surgical risk of bleeding should have their anticoagulant discontinued before surgical intervention. If they confer a high thromboembolic risk, elective surgery should be delayed until the thromboembolic risk is lower. If surgical intervention must be performed, the time period without anticoagulation should be as limited as possible, using a bridging agent such as low-molecular-weight heparin (LMWH) or UFH infusion if necessary. If the surgical risk of bleeding is low, patients can often continue their anticoagulant if at high risk of thromboembolic event without anticoagulation.

There are several patient factors that confer an increased risk of bleeding, regardless of the procedure being performed. These factors vary greatly and several attempts to quantify these risks have been made in both prospective and retrospective studies.

For patients with atrial fibrillation, a number of studies have attempted to predict bleeding complications based on patient-specific factors. The HAS-BLED score allows one to estimate the 1-year risk for major bleeding for patients with atrial fibrillation on oral anticoagulation. This score was developed based on a multivariate analysis of nearly 4000 real-world patients with atrial fibrillation on an oral anticoagulant in the Euro Heart Survey on Atrial Fibrillation (Table 3) [7]. $HEMORR_2HAGES$ is a bleeding risk scheme used to help quantify the risk of hemorrhage in elderly patients with atrial fibrillation on warfarin, based on a multivariate analysis of various patient factors of nearly 4000 patients in the National Registry of Atrial Fibrillation [8]. Last, the ATRIA study used a Cox regression model of more than 9000 patients with atrial fibrillation on warfarin to develop a simple 5-variable hemorrhage risk stratification score that was effective in quantifying the risk of warfarin-associated hemorrhage in this patient population [9].

The predictive performance of the HAS-BLED, $HEMORR_2HAGES$, and ATRIA bleeding risk scores were compared in the AMADEUS trial, which demonstrated that the HAS-BLED score more accurately predicted clinically relevant bleeding in patients with atrial fibrillation on oral anticoagulation, and was the only score to significantly improve the rate of intracranial hemorrhage in this population [10]. In the BNK Online Bridging Registry (BORDER), an observational registry of perioperative outcomes in patients undergoing invasive cardiac procedures, a HAS-BLED score of 3 or greater was the most predictive variable for bleeding [11]. The majority of these patients were receiving VKAs, which were bridged with a LMWH before the

Table 3
HAS-BLED score

Criterion	Points
Uncontrolled hypertension Systolic blood pressure >160 mm Hg	+1
Renal disease Dialysis, renal transplant, or creatinine >2.26 mg/dL	+1
Liver disease Cirrhosis or bilirubin >2× normal and AST/ALT/ALP >3× normal	+1
Stroke history	+1
Prior major bleeding or predisposition to bleeding	+1
Labile INR Unstable/high INRs, time in therapeutic range <60%	+1
Age >65	+1
Medication usage predisposing to bleeding Aspirin, clopidogrel, NSAIDs	+1
Alcohol use ≥8 drinks/wk	+1

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSAIDs, nonsteroidal anti-inflammatory drugs.

Data from Pisters, R., Lane, D.A., Nieuwlaat, R., et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. Chest 2010;138(5):p. 1093–1100.

procedure. A small retrospective case-control study was recently investigated in patients receiving DOAC (specifically rivaroxaban), in which the HAS-BLED score demonstrated a modest ability to predict major bleeding events; however, this did not reach statistical significance [12].

For patients with VTE, only the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) bleeding risk score has been shown to consistently predict major and clinically relevant bleeding at 14 days, with a score of 7 or greater indicating an increased risk of bleeding [13]. The IMPROVE bleeding risk score is a multinational observational study of more than 15,000 patients for whom a multiple regression model analysis was performed to identify risk factors at admission associated with in-hospital bleeding for patients not on therapeutic anticoagulation [14]. However, the cohort studied was limited to medical inpatients not undergoing any surgical intervention [14].

As with surgical risk of bleeding, the discontinuation of anticoagulation based on a patient's propensity for major or clinically relevant bleeding is strongly recommended, with the duration of discontinuation determined by the patient's risk of thromboembolic event while not anticoagulated.

Bridging

For patients with a high to very high thromboembolic risk (recent ischemic stroke, CHA_2DS_2-VASc score of ≥ 7, mechanical heart valve, etc) for whom anticoagulation must be discontinued for surgery with a high risk of bleeding, it may be appropriate to bridge the patient with another form of anticoagulation both preoperatively and/or postoperatively. This is especially true for patients on VKAs, who are typically instructed to hold their warfarin dose 4 to 5 days before surgery and resume it postoperatively, resulting in several days of subtherapeutic anticoagulation. Postoperative bridging may also be considered for patients who are expected to remain without oral intake owing to postoperative ileus, ventilator dependence, and so on.

If a patient with a recent VTE (ie, within 3 months) requires urgent surgical intervention and cannot be anticoagulated perioperatively, a retrievable inferior vena cava filter may be placed preoperatively, with the caveat that, once anticoagulation can be safely resumed, the inferior vena cava filter should be removed. It is important to note that the American College of Chest Physicians does not support the use of inferior vena cava filters as a means of pulmonary embolism prophylaxis in high-risk populations, such as patients with multitrauma or spinal cord injury, without evidence of deep vein thrombosis [15].

In patients with a lower risk of TE, bridging is not recommended. The Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial randomly assigned patients with a low TE risk who required interruption of warfarin for an invasive procedure to bridging with LMWH (dalteparin) versus bridging with placebo. Within 30 days, the incidence of arterial thromboembolic events were similar in the 2 cohorts, although the incidence of major bleeding was greater in those bridged with LMWH [16]. High-risk TE patients

(those with mechanical heart valves, a recent VTE, or ischemic stroke/transient ischemic attack) were excluded from this trial. Similar results were reported in a metaanalysis of 34 observational studies of patients undergoing elective surgery or procedures. The authors found that there was no significant difference in the rate of TE in patients who received bridging when compared with those that did not. However, bridging was associated with a significantly increased risk of major bleeding [17].

In the Dresden NOAC registry of 8000 patients receiving a DOAC for any indication who underwent an invasive procedure, there were similar rates of cardiovascular events regardless of whether the patient was bridged, not bridged, or oral anticoagulation was continued perioperatively. However, bridging was not found to be an independent risk factor of major bleeding in this registry [18].

The PERIOP-2 trial is a randomized, controlled trial currently investigating postoperative bridging with LMWH in patients with a mechanical heart valve, all of whom received preoperative bridging, with a primary outcome of major TE within 90 days of randomization (ClinicalTrials.gov, NCT00432796).

In general, anticoagulation bridging should be reserved for those patients who are at high or very high risk of thromboembolic events during the time of anticoagulation interruption, because bridging with LWMH or UFH does seem to confer an increased risk of major bleeding without a documented decrease in the thromboembolic events in patients with a low to moderate TE risk.

ORAL ANTICOAGULANT AGENTS

Since the FDA approval of DOACs in 2010, there has been an approximate 10-fold increase in the number of prescription of DOACs, with a concurrent 4.5-fold decrease in the number of warfarin prescriptions, for adults with nonvalvular atrial fibrillation who filled a new prescription for an anticoagulant between 2010 and 2017 [19]. Among the DOACs, the predominant anticoagulant of choice varies with time as additional prospective studies are performed comparing the DOACs not only with VKAs, but also with other DOACs. Given the prescribing patterns favoring DOACs over VKAs, it is imperative that surgeons understand the properties of the most commonly used DOACs and how these agents affect the perioperative management of anticoagulation in the current era (see Table 3).

Warfarin

Warfarin inhibits a vitamin K-dependent enzyme, preventing the production of factors II, VII, IX, and X. It has a half-life of 36 to 42 hours, and thus is generally held for 4 to 5 days before elective surgery to allow the prothrombin time/international normalized ratio (INR) to normalize [20]. If the INR is still elevated before surgery, low doses of oral vitamin K (1–2 mg) can be administered to quicken the normalization of the INR. Just as it takes several days for the reversal of warfarin's anticlotting effect, it takes several days to achieve

therapeutic anticoagulation. Postoperatively, warfarin can typically be resumed within 12 to 24 hours after surgery at the preoperative dose, assuming hemostasis was achieved intraoperatively. This step allows for therapeutic anticoagulation within a few days postoperatively. For patients at particularly high risk of TE, a bridging agent such as UFH or LMWH may be necessary in the interim, until the INR reaches the desired therapeutic goal.

In the event of minor bleeding, a dose of warfarin may be held, or low-dose vitamin K can be administered if there is a high risk of bleeding or if the INR is supratherapeutic [21]. Clinical trials involving phytonadione, a vitamin K derived from plants, showed that oral administration in conjunction with temporary interruption of warfarin can decrease an INR of 6 to 10 to less than 4 in approximately 1.4 days, assuming normal hepatic function [22]. For intravenous (IV) administration of phytonadione, this time frame is reduced to approximately 24 hours, and the decrease in the INR begins within 2 hours of administration [22]. In the event of clinically significant bleeding or major bleeding, warfarin should be held, vitamin K should be administered to aid in normalization of the INR, and fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) should be transfused for temporary reversal of warfarin's effect. Although FFP remains the most widely used coagulation factor replacement product for urgent and emergent reversal of warfarin [23], studies have shown that PCC is more effective in correcting INR when compared with FFP. A systematic review and metaanalysis of PCC versus FFP for warfarin reversal in patients on warfarin for various indications requiring reversal owing to warfarin-related, clinically relevant bleeding has been performed. This comprehensive study showed that PCC use was associated with a significant decrease in all-cause mortality at 30 days, a greater likelihood of achieving INR normalization, a shorter time to INR correction (mean difference of <6.5 hours), and a lower risk of volume overload, all when compared with the use of FFP [24]. There was no statistically significant difference in the risk of TE or achievement of hemostasis between the 2 groups.

Dabigatran

Dabigatran (Pradaxa) is an oral direct thrombin competitive inhibitor, preventing thrombin from converting fibrinogen to fibrin. Dabigatran has a rapid but predictable anticoagulation effect, reaching peak plasma levels within 1 to 2 hours of ingestion, with a half-life of 12 to 17 hours. In patients with mild to moderate renal insufficiency (creatinine clearance [CrCl] of 30–60 mL/min), the half-life increases to 15 to 18 hours, whereas for those with severe renal insufficiency (CrCl of <30 mL/min), the half-life approaches 24 to 28 hours. Dosing recommendations for the treatment of nonvalvular atrial fibrillation and VTE previously treated with 5 days of parenteral anticoagulation are as follows: 150 mg twice daily for CrCl greater than 30 mL/min and 75 mg twice daily for CrCl between 15 and 30 mL/min [25].

Perioperatively, dabigatran has been shown to have similar rates of thromboembolic events when compared with warfarin with a comparable

perioperative bleeding risk. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial studied periprocedural thromboembolic risk in 4591 patients undergoing elective procedures or surgery and found similar rates of cerebrovascular events, cardiovascular death, and pulmonary embolus between those treated with dabigatran and those treated with warfarin [26]. The RE-COVER II trial reported similar rates of periprocedural bleeding between dabigatran and warfarin, including patients undergoing urgent surgery [27].

Based on its short half-life, dabigatran may be discontinued 2 to 3 days before operative intervention in patients with normal or mildly impaired renal function, and 3 to 4 days before if moderate to severe renal impairment is present. Additionally, dabigatran can be initiated postoperatively, when a patient is safe to be therapeutically anticoagulated. Given its rapid onset of action and short life, bridging therapy is typically not indicated.

Unlike the prothrombin time/INR for warfarin, routine coagulation studies have not been validated for measuring the anticoagulation effect of dabigatran. A prolonged activated partial thromboplastin time likely indicates therapeutic levels of dabigatran; however, a normal activated partial thromboplastin time does not exclude therapeutic dabigatran levels [28].

In patients on dabigatran with clinically relevant or major bleeding, idarucizumab (Praxbind) may be used to reverse the effects of dabigatran. Approved by the FDA in 2015, idarucizumab is a monoclonal antibody that binds dabigatran, which can be used to decrease clinically relevant or major bleeding, or to reverse its anticoagulation effect in patients that may need to undergo emergent surgical intervention. The RE-VERSE AD prospective cohort study showed that idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes [29]. Idarucizumab has a half-life of 47 minutes to 10.3 hours, with a mean clearance time of 6 hours. The recommended dosing is idarucizumab 5 g IV via 2 consecutive 2.5-g infusions, and the dosing does not need to be adjusted for those with renal insufficiency. Common adverse effects include hypokalemia, constipation, hypersensitivity reactions, and thromboembolic events [30].

Rivaroxaban

Rivaroxaban (Xarelto) is an oral direct factor Xa inhibitor, inhibiting the degradation of fibrinogen to fibrin and inactivating platelets. Rivaroxaban is rapidly absorbed and largely albumin bound, reaching peak plasma levels within 2 to 4 hours and with a half-life of 5 to 9 hours. It is metabolized by the liver and excreted predominantly in the urine (66%) and feces (28%). Dosing recommendations for the treatment of nonvalvular atrial fibrillation are as follows: 20 mg once daily with meals for a CrCl of greater than 50 mL/min, and 10 mg once daily with meals for a CrCl between 15 and 50 mL/min. For the treatment of VTE, and to prevent VTE recurrence, rivaroxaban is dosed as 15 mg every 12 hours for 21 days, followed by 20 mg once daily for at least 3 months [31].

Perioperatively, rivaroxaban has been shown to have similar rates of thromboembolic events when compared with warfarin. The ROCKET AF trial compared rivaroxaban with warfarin for the treatment of nonvalvular atrial fibrillation in which patients had temporary interruptions in anticoagulation. The results showed similar thromboembolic risk and similar major bleeding risk between patients experiencing temporary interruptions in anticoagulation with rivaroxaban versus warfarin [32]. The EINSTEIN studies compared the use of rivaroxaban versus LMWH followed by warfarin for the treatment of VTE. The results were significant for similar thromboembolic rates with a decrease in major bleeding events, most noticeably intracranial bleeding [33].

Based on its short half-life, rivaroxaban may be discontinued 48 hours before surgical interventions with a high risk of bleeding, assuming normal renal function, and be restarted postoperatively as soon as hemostasis is ensured. If moderate to severe renal impairment is present, rivaroxaban should be discontinued 72 to 96 hours preoperatively. Given its rapid onset of action and short life, bridging therapy is typically not indicated.

Although rivaroxaban may prolong the prothrombin time and the activated partial thromboplastin time, the most accurate measure of rivaroxaban activity is a calibrated anti-Xa assay, which can exclude clinically significant levels of circulating rivaroxaban [34].

In patients on rivaroxaban with clinically relevant or major bleeding, or needing to undergo an emergent surgical procedure, recombinant coagulation factor Xa (Andexxa) may be used to reverse the effects of rivaroxaban. Approved by the FDA in May of 2018, recombinant coagulation factor Xa is a recombinant coagulation factor Xa shown to reduce anti-factor Xa activity by 97% in those receiving rivaroxaban 20 mg once daily, compared with an 18% decrease in the placebo group. This reversal was noted to take effect within 2 to 5 minutes of an recombinant coagulation factor Xa bolus. This reversal activity persisted for 1 to 2 hours after completion of the infusion, and was associated with restored thrombin generation previously inhibited by treatment with rivaroxaban. No serious or severe adverse events occurred, and no thrombotic events were reported in this randomized, double-blind, placebo-controlled trial [35].

Two dosing regimens for recombinant coagulation factor Xa are approved based on the direct factor Xa inhibitor administered, the dosing, and the time of last dose administered (Table 4). The low-dose regimen consists of an initial IV bolus of 400 mg at 30 mg/min, followed by an infusion of 4 mg/min for up to 120 minutes. The high-dose regimen consists of an initial IV bolus of 800 mg at 30 mg/min, followed by an infusion of 8 mg/min for up to 120 minutes. If a rivaroxaban dose of greater than 10 mg was administered within the last 8 hours, the high-dose regimen should be administered. Otherwise, for rivaroxaban 10 mg or less, the low-dose regimen should be administered [36].

Apixaban

Apixaban (Eliquis) is also an oral direct factor Xa inhibitor and works by the same mechanism as rivaroxaban. It is available as an oral formulary with a

Table 4
Oral anticoagulant summary

Oral anticoagulant		Dosing	Perioperative management	Reversal agent	Reversal dosing
Warfarin					
MOA	VKA, inhibits coagulation factor production	Daily dosing titrated to specific INR goal: INR 2–3 (VTE, atrial fibrillation) INR 2.5–3.5 (prosthetic valve)	Hold 4–5 d preoperatively, check INR Resume immediately postoperatively if hemostasis achieved May require bridging agent if high or very high thromboembolic risk given long onset of action	Minor bleeding or planned surgery: Hold dose(s), vitamin K PO Major bleeding or emergent surgery: PCC or FFP	INR $\geq$1.5 but <1.9: 1 mg PO INR >1.9 but $\leq$5.0: 1–2.5 mg PO INR >5.0 but $\leq$9.0: 2.5–5 mg PO INR >9.0: 2.5–5 mg PO and 2 U FFP 4 units FFP, vitamin K 10 mg IV slow infusion, repeat PRN
Half-life	36–42 h				
Time of onset	3–5 d				
Clearance	Renal				
Dabigatran (Pradaxa)					
MOA	Direct thrombin inhibitor	CrCl >30 mL/min: 150 mg BID CrCl 15–30 mL/min: 75 mg BID	Hold 2–3 d preoperatively if normal renal function, 3–4 d if moderate to severe renal impairment Resume postoperatively once safe to resume therapeutic anticoagulation Bridging only required if patient to remain NPO and moderate to high risk of TE	Idarucizumab (Praxbind) Effect within minutes, therapeutic ~6 h Indicated for major bleeding or emergent surgery	5 mg IV via 2.5 mg IV infusions ×2
Half-life	12–17 h				
Time of onset	1–2 h				
Clearance	Renal				

(*continued on next page*)

Table 4
(*continued*)

Oral anticoagulant		Dosing	Perioperative management	Reversal agent	Reversal dosing
Rivaroxaban (Xarelto)					
MOA	Direct factor Xa inhibitor	Atrial fibrillation: CrCl >50 mL/min: 20 mg/d CrCl 15–50 mL/min: 10 mg daily VTE: 15 mg BID ×21 d, then 20 mg/d for ≥3 mo	Hold 2 d preoperatively if normal renal function, 3–4 d if moderate to severe renal impairment Resume postoperatively once safe to resume therapeutic anticoagulation Bridging only required if patient to remain NPO and moderate to high risk of TE	Recombinant coagulation factor Xa (Andexxa) Effect within 2–5 min, therapeutic 1–2 h Indicated for major bleeding or emergent surgery	If rivaroxaban 20 mg and taken within last 8 h: 800 mg IV bolus at 30 mg/min, followed by 8 mg/min infusion for up to 120 min If rivaroxaban 10 mg: 400 mg IV bolus at 30 mg/min, followed by 4 mg/min for up to 120 min
Half-life	5–9 h				
Time of onset	2–4 h				
Clearance	66% Renal 28% Fecal				

Apixaban (Eliquis)					
MOA	Direct factor Xa inhibitor	Atrial fibrillation: 5 mg BID 2.5 mg BID if ≥2 of following: >80 years old Cr >1.5 mg/dL Weight <60 kg VTE 10 mg BID ×7 d, then 5 mg BID 2.5 mg BID after 6 mo of treatment for recurrence prophylaxis	Hold 1–2 d preoperatively if normal renal function, 3–4 d if moderate to severe renal impairment Resume postoperatively once safe to resume therapeutic anticoagulation Bridging only required if patient to remain NPO and moderate to high risk of TE	Recombinant coagulation Factor Xa (Andexxa) Effect within 2–5 min, therapeutic 1–2 h Indicated for major bleeding or emergent surgery	If apixaban 10 mg and taken within last 8 h: 800 mg IV bolus at 30 mg/min, followed by 8 mg/min infusion for up to 120 min If apixaban <10 mg: 400 mg IV bolus at 30 mg/min, followed by 4 mg/min for up to 120 min
Half-life	12 h				
Time of onset	3–4 h				
Clearance	27% renal				

Abbreviations: BID, 2 times per day; MOA, mechanism of action; NPO, nil per os; PO, orally; PRN, as needed.
Data from Refs [20–22,25,29–31,35–37].

longer absorption time than that of rivaroxaban, reaching peak plasma levels in 3 to 4 hours with a half-life of 12 hours. Like rivaroxaban, apixaban is metabolized by the liver; unlike rivaroxaban, renal excretion accounts for only 27% of the total drug clearance [37].

For the treatment of nonvalvular atrial fibrillation, 5 mg twice daily dosing has been shown to reduce the risk of ischemic stroke and systemic embolization. However, if the patient has at least 2 of the following characteristics, 2.5 mg twice daily dosing is recommended with the same risk reduction: older than 80 years of age, serum creatinine greater than 1.5 mg/dL, or body weight less than 60 kg [37].

Treatment of VTE is successfully achieved with a 10 mg twice daily dosing for 7 days, followed by 5 mg twice daily dosing for the remainder of the treatment period. Dosing reduction for the aforementioned patient characteristics is not indicated in the treatment of VTE. After a 6-month treatment period, 2.5 mg twice daily dosing can be continued for reduction in the risk of recurrent VTE [37].

Apixaban is also indicated for deep vein thrombosis prophylaxis after hip or knee replacement surgery. Appropriate dosing is as follows: 2.5 mg twice daily for 35 days starting 12 to 24 hours after hip replacement surgery, or 2.5 mg twice daily dosing for 12 days starting 12 to 24 hours after knee replacement surgery [37].

The ARISTOTLE study compared patients with nonvalvular atrial fibrillation treated with apixaban versus warfarin, and found that apixaban was both noninferior and superior to warfarin in thromboembolic risk reduction, with decreased rates of major bleeding events and overall decreased rate of overall mortality [38]. This study excluded patients with end-stage renal disease who are dialysis dependent, a patient population for which many physicians reduce the apixaban dose owing to renal impairment. A retrospective cohort study of 25,523 patients with dialysis-dependent -stage renal disease and atrial fibrillation treated with apixaban or warfarin showed that the standard 5 mg twice daily dosing was associated with a significantly lower risk of thromboembolic events, lower rates of death, and lower risk of major bleeding than both the reduced-dose apixaban and warfarin cohorts [39].

The perioperative management of anticoagulation interruption for patients on apixaban is very similar to that of rivaroxaban owing to its similarly short half-life. Apixaban may be discontinued 24 to 48 hours before surgical interventions with a high risk of bleeding, assuming normal renal function, and be restarted postoperatively as soon as hemostasis is ensured. If moderate to severe renal impairment is present, rivaroxaban should be discontinued 72 to 96 hours preoperatively. Given its rapid onset of action and short life, bridging therapy is typically not indicated. Data from the ARISTOTLE study show that 38% of patients did not stop apixaban before their procedure, and the postprocedure stroke and major bleeding rates were similar to those that did interrupt apixaban therapy. Thus, in low bleeding risk procedures, such as dental extractions and skin lesion excisions, apixaban may be safely continued [40].

Recombinant coagulation factor Xa is also FDA approved for the reversal of apixaban in settings of life-threatening or uncontrolled bleeding. Recombinant coagulation factor Xa was shown to reduce antifactor Xa activity by 92% in those receiving apixaban, similar to the reduction seen in patients taking rivaroxaban [35]. The low-dose and high-dose regimens apply to apixaban as well (see Table 4), with the high-dose regimen reserved only for patients taking more than 5 mg of apixaban per dose with the last administration within 8 hours [36].

FUTURE DIRECTIONS

Although there is convincing evidence to support the use of DOACs as opposed to warfarin for the treatment of VTE and atrial fibrillation, there is a lack of clinical data that directly compare the different DOACs in the perioperative setting. Additionally, the perioperative management of DOACs is largely based on the pharmacokinetics of each agent; however, these recommendations have yet to be validated by clinical trials. The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study is a proposed prospective study designed to develop and assess a standardized protocol for perioperative DOAC management that remains patient-specific [41]. Studies such as the PAUSE study have the potential to remove some of the guess work surgeons use when planning to operate on the increasing number of patients on anticoagulation therapy. And with the recent approval of very high cost reversal agents for many of the DOACs, there is a significant need to validate their efficacy in real-world clinical settings, particularly as the use of these agents become more widely adopted.

SUMMARY

With the advent of DOACs as mainstay anticoagulation therapy for a significant proportion of patients, perioperative anticoagulation management has become an increasingly challenging endeavor for many surgeons. A thorough assessment of the thromboembolic and bleeding risks is critical in navigating these patients safely through the perioperative period. The increasing use of DOACs makes it mandatory for all surgeons to become familiar with the characteristics of each agent. Several DOAC reversal agents are currently available, albeit at a very high cost. Although this article discusses general strategies to help balance the thromboembolic risks associated with interruption in anticoagulation therapy with the risks of bleeding if therapy is continued, there is clearly a need for further studies to help standardize perioperative anticoagulation management that can still be tailored to meet individual patients' needs.

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