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Perioperative Management of Patients Taking Direct Oral Anticoagulants
A Review

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IMPORTANCE Direct oral anticoagulants (DOACs), comprising apixaban, rivaroxaban, edoxaban, and dabigatran, are commonly used medications to treat patients with atrial fibrillation and venous thromboembolism. Decisions about how to manage DOACs in patients undergoing a surgical or nonsurgical procedure are important to decrease the risks of bleeding and thromboembolism.

OBSERVATIONS For elective surgical or nonsurgical procedures, a standardized approach to perioperative DOAC management involves classifying the risk of procedure-related bleeding as minimal (eg, minor dental or skin procedures), low to moderate (eg, cholecystectomy, inguinal hernia repair), or high risk (eg, major cancer or joint replacement procedures). For patients undergoing minimal bleeding risk procedures, DOACs may be continued, or if there is concern about excessive bleeding, DOACs may be discontinued on the day of the procedure. Patients undergoing a low to moderate bleeding risk procedure should typically discontinue DOACs 1 day before the operation and restart DOACs 1 day after. Patients undergoing a high bleeding risk procedure should stop DOACs 2 days prior to the operation and restart DOACs 2 days after. With this perioperative DOAC management strategy, rates of thromboembolism (0.2%-0.4%) and major bleeding (1%-2%) are low and delays or cancellations of surgical and nonsurgical procedures are infrequent. Patients taking DOACs who need emergent (<6 hours after presentation) or urgent surgical procedures (6-24 hours after presentation) experience bleeding rates up to 23% and thromboembolism as high as 11%. Laboratory testing to measure preoperative DOAC levels may be useful to determine whether patients should receive a DOAC reversal agent (eg, prothrombin complex concentrates, idarucizumab, or andexanet-α) prior to an emergent or urgent procedure.

CONCLUSIONS AND RELEVANCE When patients who are taking a DOAC require an elective surgical or nonsurgical procedure, standardized management protocols can be applied that do not require testing DOAC levels or heparin bridging. When patients taking a DOAC require an emergent, urgent, or semiurgent surgical procedure, anticoagulant reversal agents may be appropriate when DOAC levels are elevated or not available.

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Direct oral anticoagulants (DOACs), including apixaban, rivaroxaban, edoxaban, and dabigatran, are widely used anticoagulants.[1] Approximately 4 million patients in the US are currently being treated with DOAC therapy.[2] DOACs are indicated for stroke prevention in patients with atrial fibrillation and for the prevention and treatment of venous thromboembolism.[3-5] For these conditions, DOACs have advantages compared with warfarin that include a lower risk of bleeding, fixed dosing that does not require coagulation test monitoring, and fewer potential drug-drug interactions.[5]

Knowing how to advise patients who are taking a DOAC and need a surgical procedure (a surgical operation typically with general/spinal anesthetic) or nonsurgical procedure (a nonsurgical intervention, such as a biopsy or colonoscopy, that typically does not require general/spinal anesthetic) is important because approximately 20% of DOAC-treated patients undergo an elective or urgent procedure annually.[6,7] Moreover, DOAC use is increasing, especially among older patients[8,9]for whom a surgical or nonsurgical procedure is most commonly performed.[10] Perioperative DOAC management requires careful decisions about preoperative interruption and postoperative DOAC resumption to minimize the risks of thromboembolism and bleeding. Surgical-site bleeding increases the likelihood of reoperation and delays resumption of anticoagulant therapy, which increases the risk for thromboembolism.[7,11]

Recent clinical practice guidelines, including those of the European Society of Cardiology,[12] the American College of Chest Physicians,[7] the European Society of Regional Anesthesia & Pain Therapy,[13] the American Society of Regional Anesthesia and Pain Medicine,[14] and the International Union of Angiology,[15] provided evidence-based recommendations for perioperative DOAC management.

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Table 1. Clinical Indications and Dosing of Direct Oral Anticoagulants (DOACs)

DOAC	Clinical indication and standard dosing		Reduced dosing in patients with nonvalvular atrial fibrillation
	Nonvalvular atrial fibrillation	Venous thromboembolism	
Apixaban	5 mg twice daily	5 mg twice daily or 2.5 mg twice daily (after initial 3-6 mo of treatment)	Reduced dose in patients with ≥1 of: serum creatinine <133 µmol/L, age >80 y, or weight <60 kg
Dabigatran	150 mg twice daily	150 mg twice daily (requires initial 5 d of LMWH)	Reduced dose in patients >75 y or at increased risk for bleeding
Edoxaban	60 mg daily	60 mg daily (requires initial 5 d of LMWH)	Reduced dose in patients ≥1 of: creatinine clearance <50 mL/min, age >80 y, or major drug interaction
Rivaroxaban	20 mg daily	20 mg daily or10 mg daily (after initial 3-6 mo of treatment)	Reduced dose in patients with creatinine clearance <50 mL/min

Abbreviation: LMWH, low-molecular-weight heparin.

This review summarizes current evidence regarding management of DOAC therapy in patients undergoing an elective, emergent, urgent, or semiurgent surgical or nonsurgical procedure.

Methods

A search was performed of MEDLINE, Current Contents, and PubMed for English-language articles published from January 1, 2012, until March 30, 2024, using the terms *perioperative*, *direct oral anticoagulants*, *surgery*, and *invasive procedures*. A total of 298 articles was identified. We supplemented this search with a manual review of bibliographies of systematic or narrative reviews that included perioperative anticoagulation management and related clinical practice guidelines. We prioritized inclusion of recent, high-quality articles based on relevance, topics covered, rigor of study design, and randomized clinical trials when available. A total of 99 articles were included, consisting of 26 clinical trials, 30 retrospective observational studies, 28 systematic or narrative reviews, and 15 clinical practice guidelines.

DOACs and Foundations of Perioperative Management

DOAC medications exert their anticoagulant effect through inhibition of factor Xa (apixaban, rivaroxaban, and edoxaban) or factor IIa (dabigatran). DOACs have predictable pharmacokinetic and pharmacodynamic effects, with peak effects occurring 2 to 3 hours after DOAC intake.[5,16]

DOACs are indicated to treat nonvalvular atrial fibrillation and for the prevention and treatment of venous thromboembolism (**Table 1**). DOACs should not be prescribed to patients with a mechanical heart valve, antiphospholipid antibody syndrome, or atrial fibrillation associated with rheumatic heart disease, for whom vitamin K antagonists (eg, warfarin) are preferred.[17] DOACs are not recommended for use in pregnant or breastfeeding individuals because they cross the placenta and are present in breast milk and there are insufficient data about their safety for the fetus and newborn.[17] There is limited evidence on the efficacy and safety of DOAC use in patients with thrombosis at unusual locations, including left ventricular thrombosis and thrombosis of the splanchnic and cerebral sinus veins,[5,17] and on the efficacy and safety of use of apixaban, rivaroxaban, and edoxaban in patients with stage IV kidney disease (creatinine clearance [CrCl], <30 mL/min).[18,19] In these situations, DOACs may be a therapeutic option but treatment decisions should be made on an individual basis in consultation with a hematologist or cardiologist. Dabigatran is contraindicated in patients with a CrCl of less than 30 mL/min.

DOAC dosing should be reduced based on factors that affect DOAC clearance, including patient age 80 years or older, weight less than 60 kg, CrCl less than 50 mL/min, and potential DOAC-drug interactions[20,21] (Table 1). Perioperative bleeding risk does not appear to differ among DOAC medications.[22,23]

DOAC Mechanisms of Action and Clinical Pharmacology

DOAC elimination half-lives are used to determine how long a DOAC should be withheld to ensure minimal or no residual anticoagulant effect at the time of an elective surgical or nonsurgical procedure (**Table 2**). Elimination half-lives of factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) are 8 to 12 hours in patients with a CrCl above 30 mL/min.[16,20] Dabigatran has a higher dependence on kidney clearance, so its elimination half-life is 10 to 14 hours in patients with a CrCl at or above 50 mL/min and 18 to 24 hours in patients with a CrCl of 30 to 49.9 mL/min.[7,16]

DOAC medications have rapid onset of anticoagulant effect (peak onset of action: 2-3 hours after intake),[16] which may increase the risk for bleeding after a surgical or nonsurgical procedure. Therefore, DOAC resumption should be adjusted according to the bleeding risk associated with the surgery or procedure and should be delayed if there is postoperative bleeding or uncertainty about surgical-site hemostasis.[6] DOAC medications have a rapid onset of anticoagulation, and because the typical length of DOAC cessation perioperatively is short (eg, 2-4 days), the risk of thromboembolism associated with DOAC cessation in the perioperative period is low (eg, <0.5%).[7,11,24]

Perioperative Anticoagulation Clinical Care Delivery

Perioperative anticoagulant management may involve family physicians, internists, surgeons, anesthesiologists, and pharmacists. Facilitating communication and management consensus among members of the health care team can help prevent surgical or nonsurgical procedure cancellations and improve patient understanding and satisfaction.[25-32] Standardized anticoagulation protocols, some of which are available as point-of-care online tools (thrombosiscanada.ca, mappp.ipro.org, anticoagulationtoolkit.org), can be integrated into electronic medical records as clinical decision support tools.[28] Anticoagulation clinics, whether undertaken with in-person or virtual care models, can enhance interdisciplinary communication and address patient questions and concerns about anticoagulant medications.[29-31]

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Table 2. Direct Oral Anticoagulant (DOAC) Pharmacologic Properties

DOAC	Mechanism of action	Elimination half-life ($t_{1/2}$), h	Peak action (t_{max}), h	Kidney clearance, %	Potential drug interactions	Reversal agents
Apixaban	Factor Xa inhibition	9-11	2-3	25	Inhibitors[a] and inducers[b] of P-gp and CYP3A43	Andexanet-α or PCC
Dabigatran	Factor IIa inhibition	12-14[c]	2-3	80	Inhibitors[a] and inducers[b] of P-gp	Idarucizumab, PCC, or activated PCC
Edoxaban	Factor Xa inhibition	10-14	2-3	50	Inhibitors[a] and inducers[b] of P-gp	Andexanet-α or PCC
Rivaroxaban	Factor Xa inhibition	9-11	2-3	33	Inhibitors[a] and inducers[b] of P-gp and CYP3A43	Andexanet-α or PCC

Abbreviations: CYP, cytochrome P; P-gp, P-glycoprotein; PCC, prothrombin complex concentrates.

[a] Inhibitors of P-gp and/or CYP3A43, which may increase the bioavailability of DOACs and have the potential to increase bleeding risk include antifungal drugs (ketoconazole, itraconazole), antiviral drugs (ritonavir), dronedarone, verapamil, macrolide antibiotics (clarithromycin, azithromycin), tamoxifen, kinase inhibitors, and immunosuppressant drugs (cyclosporine, tacrolimus).

[b] Inducers of P-gp and/or CYP3A43, which may decrease the bioavailability of DOACs and have the potential to increase thrombosis risk include rifampin, anticonvulsant drugs (phenytoin, carbamazepine, phenobarbital), dexamethasone, doxorubicin, vinblastine, enzalutamide, and St. John's wort.

[c] Elimination half-life of 18-24 hours in patients with a creatinine clearance of 30-50 mL/min.

Patients Undergoing an Elective Surgical or Nonsurgical Procedure

When selecting a therapeutic plan for perioperative DOAC management, clinicians should categorize the risk of bleeding associated with an elective surgical or nonsurgical procedure into categories of minimal risk, low to moderate risk, and high risk. Although a standardized DOAC interruption and resumption protocol can be recommended based on this bleeding risk classification (**Figure 1**),[7,11,24] other factors that may affect bleeding risk, such as a prior history of bleeding and active cancer, should also be considered.[23,28]

Perioperative DOAC Continuation for Minimal-Risk Elective Procedures

Recent studies have supported DOAC continuation in patients undergoing procedures associated with minimal bleeding risk. A prospective study of 846 patients undergoing catheter ablation of nonvalvular atrial fibrillation reported that rates of a composite end point of symptomatic thromboembolism and major bleeding events within 30 days of the procedure were 0.7% in patients who did not stop DOACs and 1.2% in patients who stopped DOACs for surgery (P = .48).[33] In 737 patients who underwent pacemaker or internal cardiac defibrillator implantation or atrioventricular node ablation with DOAC continuation, the incidence of device pocket hematoma or other major bleeding was 1.3% to 2.1%.[33-36] In a retrospective cohort study of 112 patients, compared with temporary DOAC interruption, there was no increase in major bleeding in patients who continued DOACs on the day of minor skin procedures.[37] In 2 meta-analyses that included 988 patients undergoing minor dental procedures who were taking a DOAC,[38,39] there was no increase in major bleeding in patients who continued DOACs, compared with temporary DOAC interruption. In retrospective studies that included a total of 114 patients who did not discontinue DOACs prior to phacoemulsification (cataract) surgery performed with topical anesthesia, the incidence of procedure-site bleeding was 0% to 1.8%.[40-42]

DOAC Discontinuation for Elective Surgical or Nonsurgical Procedures

For patients undergoing a minimal bleeding risk procedure, such as a dental extraction or skin lesion removal, those taking a once-daily DOAC can delay the morning dose until the evening postprocedure and patients taking a twice-daily DOAC can omit the morning dose. Alternatively, the DOAC can be discontinued on the day of the procedure if there is concern about excessive bleeding (Figure 1).

Patients undergoing a low-to-moderate bleeding risk surgical or nonsurgical procedure, such as cholecystectomy or inguinal hernia repair, should typically discontinue DOACs 1 day before the procedure, corresponding to a 30- to 36-hour (approximately 3 half-lives) interval between the last dose and the procedure to minimize any residual anticoagulant effect at the time of the procedure or operation. Patients undergoing a high bleeding risk procedure, such as major joint replacement or cancer surgery, who are taking a factor Xa inhibitor DOAC (apixaban, rivaroxaban, or edoxaban) require a 2-day period of DOAC cessation prior to surgery, which corresponds to a 60- to 68-hour (approximately 5 half-lives) interval between the last dose and the procedure. Compared with dabigatran-treated patients with a CrCl of 50 mL/min or above, patients receiving a factor IIa inhibitor DOAC who have a CrCl of less than 50 mL/min should stop dabigatran for 1 additional day prior to a low-to-moderate–risk surgery and 2 additional days prior to a high bleeding risk surgery (Figure 1) (**Box**).

The above-mentioned strategy was studied in a prospective perioperative management study (PAUSE) that enrolled 3007 DOAC-treated patients with atrial fibrillation and a CrCl of greater than 30 mL/min who underwent an elective surgical or nonsurgical procedure. The cohort included 1257 (41.8%) patients taking apixaban, 668 (22.2%) taking dabigatran, and 1082 (36.0%) taking rivaroxaban.[43] This cohort included 1007 patients (33.5%) who underwent a high bleeding risk procedure. In this study, patients were managed with a standardized perioperative DOAC protocol outlined in Figures 1 and **2** and did not receive heparin bridging.[43] The 30-day postoperative rate of major bleeding was 1.35% (95% CI, 0%-2.00%) in the apixaban cohort, 0.90% (95% CI, 0%-1.73%) in the dabigatran cohort, and 1.85% (95% CI, 0%-2.65%) in the rivaroxaban cohort. Arterial thromboembolism (transient ischemic attack, stroke, and systemic embolism) was 0.16% (95% CI, 0%-0.48%) in the apixaban cohort, 0.60% (95% CI, 0%-1.33%) in the dabigatran cohort, and 0.37% (95% CI, 0%-0.82%) in the rivaroxaban cohort. In patients with a high bleeding-risk procedure, the rates of major bleeding were 2.96% (95% CI, 0%-4.68%)

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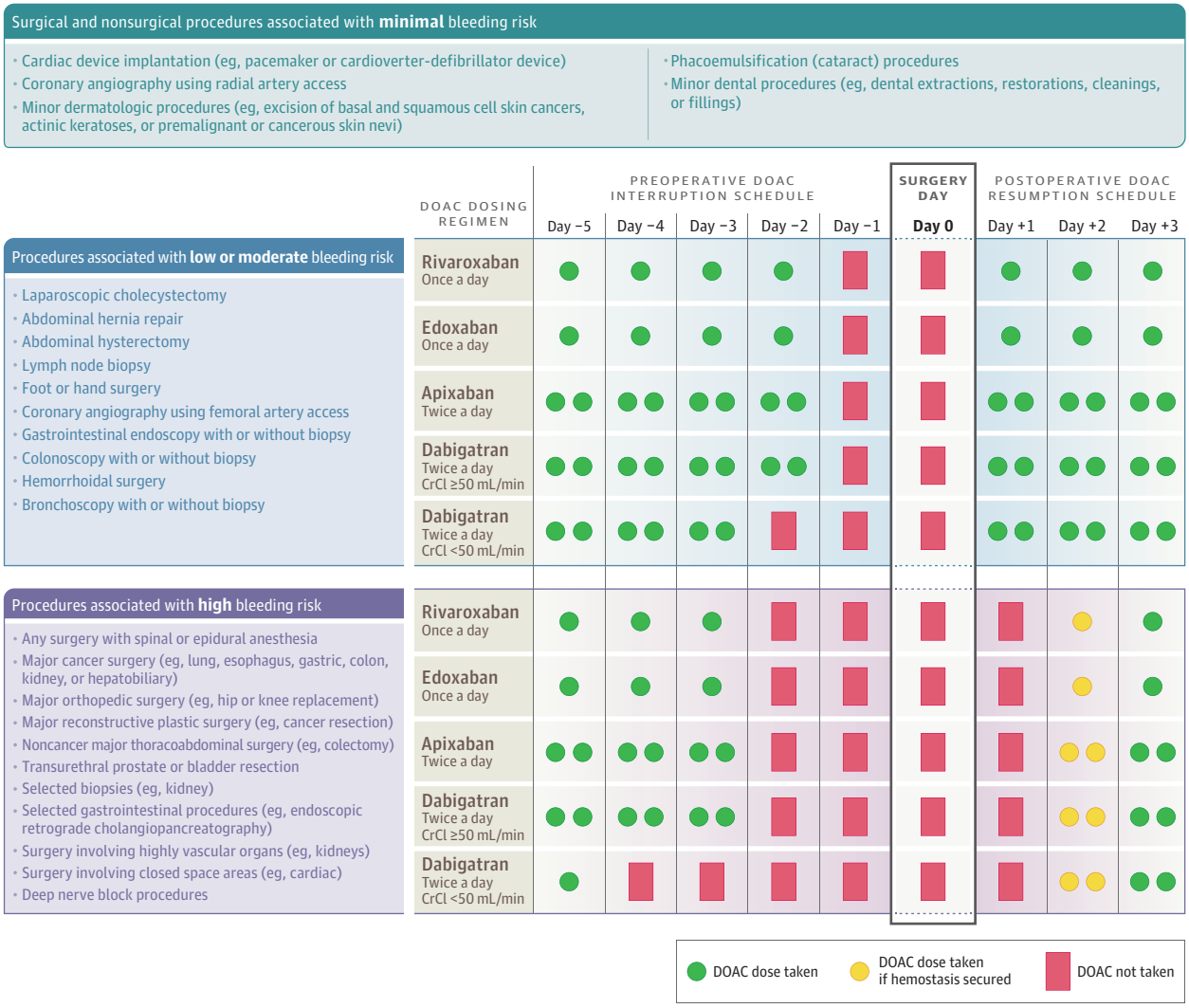
Figure 1. Perioperative Direct Oral Anticoagulant (DOAC) Dosing Schedule



CrCl indicates creatinine clearance.

in the apixaban cohort, 0.88% (95% CI, 0%-2.62%) in the dabigatran cohort, and 2.95% (95% CI, 0%-4.76%) in the rivaroxaban cohort.

A prospective, multicenter registry of perioperative DOAC management in 422 patients for whom DOAC interruption was determined by the treating physician (and varied between 1-218 hours) reported that after a 49 to 72–hour interruption interval, 95% of patients had a preoperative DOAC level less than 30 ng/mL, similar to 94.1% of patients in the PAUSE study with DOAC levels less than 30 ng/mL after a 60 to 68–hour interruption.[44,45] A retrospective single-center study assessed perioperative management in 525 DOAC-treated patients undergoing an elective surgery or procedure. Unlike the PAUSE study, perioperative DOAC management was not standardized in this study and was decided by the treating physician.[46] With this approach, 2.4% of patients developed major bleeding and 0.8% had arterial thromboembolism, which are higher rates than observed in the PAUSE study.[43]

Postoperative DOAC Resumption

The timing of postoperative DOAC resumption is based on the risk of bleeding associated with the surgical or nonsurgical procedure and an assessment of surgical-site hemostasis, including blood loss at surgical-site dressings and drains. In the PAUSE study, DOACs were resumed no earlier than 24 hours after a low-to-moderate–risk surgical or nonsurgical procedure and 48 to 72 hours after a high bleeding risk procedure with allowances for an extended delay in DOAC resumption of 2 to 3 days for some patients (eg, those with ongoing hematuria following radical prostatectomy) or if there was concern about surgical-site bleeding after cardiac, intracranial, or spinal surgery. This approach was associated with a 0.9% (95% CI, 0%-1.32%) rate of 30-day postoperative bleeding in patients with low-to-moderate bleeding risk and with a 2.48% (95% CI, 0%-3.43%) rate in patients with a high risk of bleeding.[23,43] For patients undergoing a surgical or nonsurgical procedure with a high risk of bleeding who were at increased

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Box. Commonly Asked Questions About Perioperative Management of Direct Oral Anticoagulants (DOACs)

1. How should DOACs be managed for patients undergoing minor, office-based procedures, such as dental extractions or cleaning or skin lesion removal?

Most minor, office-based procedures can be completed safely without discontinuing DOACs. However, to avoid high DOAC levels in close proximity to a procedure, it is advisable to withhold the morning DOAC dose for patients taking a twice-daily DOAC (apixaban, dabigatran) and to delay until evening the dose for patients taking a once-daily DOAC (rivaroxaban, edoxaban).

2. How should DOACs be managed for patients undergoing a colonoscopy?

Most colonoscopy procedures are associated with a low risk for bleeding. DOACs can be paused 1 day before the procedure and on the day of the procedure. For individuals who undergo removal of a large (>1 cm) polyp or multiple polyps, it is advisable to delay the resumption of the DOAC for an additional 1 to 2 days after colonoscopy.

3. How should DOACs be managed for patients undergoing a major surgical procedure that requires at least overnight hospitalization?

Most surgical procedures that require hospitalization for at least 1 night are classified a high bleeding risk, including hip or knee replacements; major cancer surgery; cardiac, neurosurgical, or spine surgery; or any operation with neuraxial (spinal/epidural) anesthesia. For these patients, it is advised to withhold DOACs for 2 days before surgery and at least 2 days after. If there is ongoing bleeding or concern about bleeding within certain anatomic areas (pericardial, intracranial), an additional 1 to 3 days of postoperative DOAC interruption is advisable until it is deemed safe to resume the DOAC.

risk for postoperative venous thromboembolism, the PAUSE study allowed patients to receive a prophylactic, low-dose low-molecular-weight heparin (LMWH) regimen (eg, dalteparin 5000 IU daily, enoxaparin 40 mg daily) for 1 to 3 days until the DOAC was resumed.

Perioperative DOAC Level Measurements

Few data exist on the effect of measuring preoperative DOAC levels on perioperative bleeding risk. A preoperative DOAC level considered safe to allow surgery, especially surgery associated with high bleeding risk, is not established. A DOAC level of less than 50 ng/mL may be considered a minimal, clinically insignificant anticoagulant effect, and a DOAC level of less than 30 ng/mL may be considered an undetectable level. In the PAUSE study,[43] 2540 (85%) patients underwent DOAC level testing just before their elective surgical or nonsurgical procedure, although this testing was not available for clinical use. With this standardized perioperative management, more than 90% of all patients had a preoperative DOAC level less than 50 ng/mL; in a patient subgroup with a high risk of bleeding, 98.9% had a residual DOAC level less than 50 ng/mL and 94.7% had a level less than 30 ng/mL.[43] A subanalysis of PAUSE found no significant association between preoperative DOAC levels (<30 ng/mL, 30-50 ng/mL, or >50 ng/mL) and perioperative major or nonmajor bleeding.[23] Guidelines from the American College of Chest Physicians recommend against routine use of DOAC level testing before an elective procedure due to uncertainty about the clinical importance of DOAC levels and because many medical centers do not have the capacity to measure DOAC levels.[7] DOAC level testing may be useful before emergent, urgent, or semiurgent surgery, as discussed below.

Perioperative Heparin Bridging

In warfarin-treated patients, an LMWH medication is typically administered for 3 to 4 days before and 4 to 5 days after an operation to minimize the amount of time patients are not fully anticoagulated in the perioperative period, when warfarin treatment is initially withheld and then resumed. However, compared with warfarin, the anticoagulant effect of DOACs decreases more rapidly after interruption and is reestablished more quickly after resumption,[16] thereby obviating the need for perioperative LMWH bridging during perioperative DOAC interruption. The American College of Chest Physicians practice guidelines recommend against heparin bridging during perioperative DOAC interruption because this practice increases the risk of bleeding, which can delay the resumption of anticoagulation and thereby potentially increase the risk of arterial thromboembolism.[7,47,48] In DOAC-treated patients who required an elective surgery/procedure, LMWH bridging was associated with an increased risk of bleeding compared with no bridging (6.8% vs 1.8%; $P < .001$) and did not reduce the risk of arterial thromboembolism (0.5% vs 0.3%; $P = .46$).[49]

For patients undergoing a high bleeding risk operation associated with a high risk of venous thromboembolism (eg, major cancer surgery, spinal surgery, or hip/knee replacement surgery), low-dose (prophylactic) LMWH (eg, dalteparin 5000 IU daily or enoxaparin 40 mg daily) should be started within 24 hours postoperatively and continued for 2 to 3 days before resumption of DOACs.[50]

Special Considerations for Patients Taking DOACs Undergoing Elective Surgical Procedures

Patients With Impaired Kidney Function

The management strategy outlined in Figure 1 is applicable to patients with a CrCl at or above 30 mL/min, recognizing that some of these patients are receiving a lower-dose DOAC regimen adjusted for impaired kidney function.[51] However, in patients with severe kidney insufficiency (CrCl, 15-29 mL/min) or end-stage kidney disease (CrCl, <15 mL/min), there are limited data on DOAC pharmacokinetics and the timing of preoperative DOAC interruption is uncertain.[51,52] Therefore, for patients with CrCl of less than 30 mL/min, expert opinion recommends extending DOAC interruption for 3 to 4 days instead of 2 days before surgery. Dabigatran is contraindicated in patients with a CrCl of less than 30 mL/min; patients with a CrCl of 30 to 50 mL/min who are taking dabigatran should stop this medication for an additional 1 to 2 days before surgery to allow clearance of dabigatran.

Patients Undergoing Neuraxial (Spinal or Epidural) Anesthesia

For individuals undergoing neuraxial anesthesia or procedures, the American Society of Regional Anesthesia and Pain Medicine recommends that DOACs be discontinued for 3 days preoperatively if patients are taking apixaban, edoxaban, or rivaroxaban and 4 days preoperatively if patients are taking dabigatran. The European Society of Regional Anesthesia & Pain Therapy recommends at least a 72-hour DOAC interruption prior to a surgical or nonsurgical

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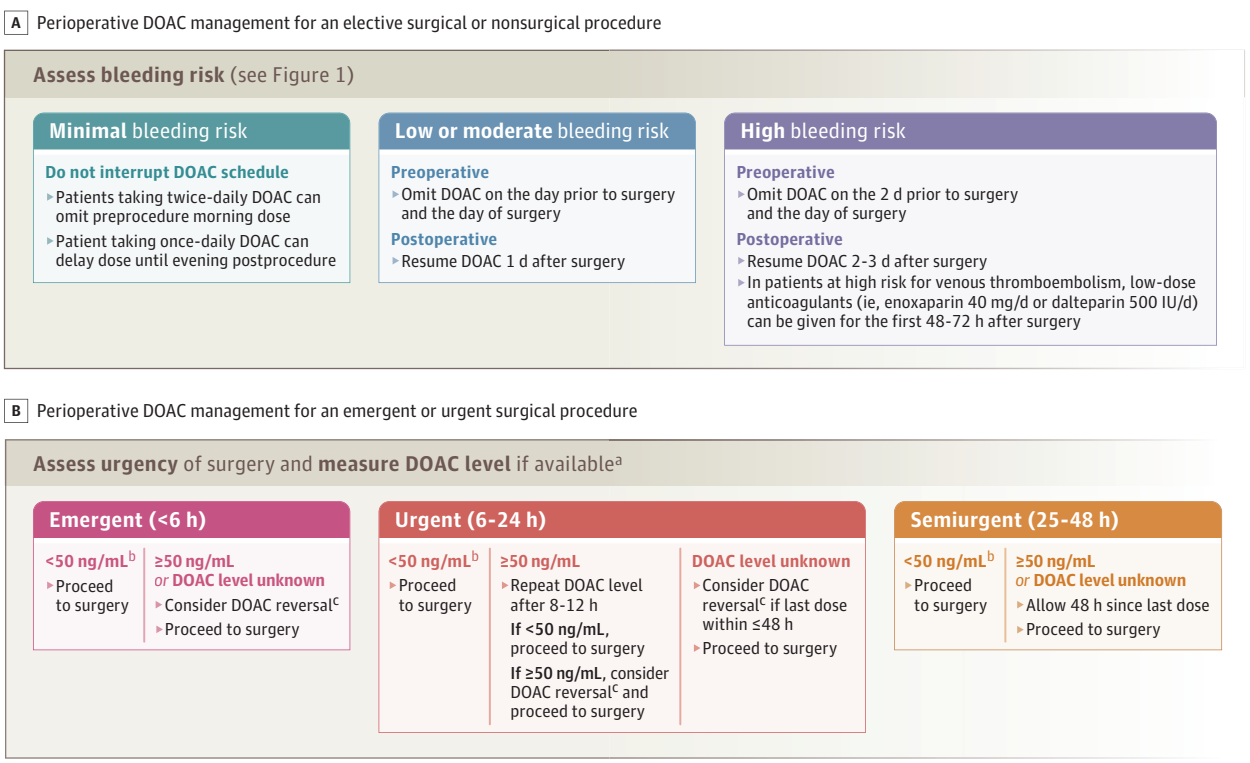
Figure 2. Approach to Perioperative Direct Oral Anticoagulant (DOAC) Management for Elective, Emergent, or Urgent Surgical or Nonsurgical Procedures



[a]Anti–factor Xa assays for apixaban, edoxaban, and rivaroxaban and dilute thrombin time for dabigatran.

[b]For dilute thrombin time, <50 seconds.

[c]DOAC reversal agents comprise prothrombin complex concentrates, idarucizumab (only for patients receiving dabigatran), and andexanet-α (only for patients receiving apixaban, edoxaban, or rivaroxaban).

procedure[13,14,53] to minimize the risk for epidural bleeding, a rare but devastating complication that can result in lower limb paralysis.[54] These recommendations also apply to patients undergoing epidural steroid injections and sympathetic ganglion blocks.

Patients Undergoing Dental Procedures

Dental procedures, such as tooth extractions, endodontic procedures (eg, root canals), and dental cleaning, are common and may be associated with bleeding at the procedure site. Bleeding can be minimized by delaying or omitting the DOAC dose on the day of the procedure and by providing adequate procedure site pressure. Oral tranexamic acid, an antifibrinolytic agent used to prevent bleeding after major surgery, can be administered as a mouthwash (500 mg tablet crushed in 5-10 mL warm water) 3 to 4 times daily postprocedure in patients undergoing dental procedures when bleeding is anticipated.[55-57]

Patients Undergoing Endoscopy

Colonoscopy and other gastrointestinal endoscopic procedures are common procedures that require anticoagulant management[58] and are considered low-to-moderate bleeding risk. However, certain procedures, such as removal of a large (>1 cm) polyp or endoscopic retrograde pancreatography with sphincterotomy, are considered high bleeding risk. These procedures require DOAC interruption for 1 additional day preprocedure and 1 to 2 days postprocedure (4-5 days of DOAC interruption in total) compared with a 2-day DOAC interruption for low-to-moderate bleeding risk procedures[59-61] (Figure 1).

Patients Unable to Resume Oral Medications in the Early Postoperative Period

For patients who have undergone major intra-abdominal or bowel surgery or who develop postoperative gastroparesis or intestinal ileus and are unable to resume oral medications for 2 to 4 days, a low-dose LMWH regimen (such as dalteparin 5000 IU daily or enoxaparin 40 mg daily) should be used as thromboprophylaxis until oral medications can be resumed. Therapeutic-dose LMWH is not recommended due to increased risk of postoperative bleeding.[62]

Emergent, Urgent, or Semiurgent Surgical Procedures

Emergent surgical procedures are typically performed within 6 hours of clinical presentation and include surgery for a ruptured or obstructed viscus or surgery for bleeding that is life-threatening or at a critical site (eg, intracranial aneurysm rupture). Urgent surgical procedures are typically performed within 24 hours of clinical presentation and include surgery for lower or upper limb fractures or acute limb ischemia. Semiurgent surgical or nonsurgical procedures are less well defined, but include conditions such as acute cholecystitis or diverticulitis, nonseptic abscesses, or stable malignant or nonmalignant effusion that can be initially treated medically followed by surgical or percutaneous procedures.

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Emergent or Urgent Surgical Procedures

Patients treated with DOACs who require emergent or urgent surgical procedures have a high risk of bleeding (17%-23%) and venous and arterial thromboembolism (7%-16%).[63-65] The anticoagulant effect of a DOAC can be neutralized with DOAC-specific reversal agents, including andexanet-α for apixaban, edoxaban, and rivaroxaban[64] or idarucizumab, a monoclonal antibody fragment that acts as a specific reversal agent for dabigatran.[66] Prothrombin complex concentrate (PCC) and activated PCC, which are nonspecific prohemostatic agents, can be used to reverse the effect of all DOACs.[64] DOAC reversal agents are expensive: andexanet-α ranges from $10 000 to $12 000, idarucizumab from $5000 to $6000, and prothrombin complex concentrates and activated PCC from $4000 to $7000.[67-69] The cost-effectiveness of DOAC reversal in the perioperative setting has not been studied. A 2024 study assessing andexanet-α in 530 patients with intracerebral hemorrhage found that compared with usual care (85.5% received PCC), andexanet-α was associated with better hemostatic efficacy (67.0% vs 53.1%; $P = .003$), but also with a significant increase in ischemic stroke and thrombotic events (10.3% vs 5.6%; $P = .048$), suggesting andexanet-α should be administered with caution in patients with prior stroke or thrombosis.[70]

The REVERSE-AD study enrolled 202 patients taking dabigatran who underwent an urgent procedure and received anticoagulant reversal with 5 g of intravenous idarucizumab.[66] This study reported normal periprocedural hemostasis in 93.4% of patients, mildly abnormal hemostasis in 5.1%, and moderately abnormal hemostasis in 1.5%; the 90-day thrombotic event rate was 7.4%.[66] A single-center retrospective study of 44 patients taking DOACs prior to admission (27 [62.8%] apixaban and 16 [37.2%] rivaroxaban) reported 30 (78.9%) patients had excellent or good hemostasis within 24 hours after periprocedural administration of andexanet-α.[71] In a retrospective study of 85 patients with major bleeding (33 treated with andexanet-α and 52 treated with 4-factor PCC), effective hemostasis was similar in both groups (84.8% vs 76.9%; $P = .373$) and thrombotic events during hospitalization were more frequent in the andexanet-α group (18%) vs 4-factor PCC (3.8%; $P = .027$).[72] A cohort study reported outcomes of 84 patients taking rivaroxaban or apixaban who had major bleeding and required an urgent intervention and were treated with PCC.[73] PCC was considered effective in 58 (69.1%) patients and ineffective in 26 (30.9%) patients, of whom 16 (61.5%) had intracerebral hemorrhage; 2 patients developed ischemic stroke after treatment with PCC.

DOAC Management for Emergent, Urgent, or Semiurgent Surgical Procedures

Management decisions for patients taking DOACs who need emergent, urgent, or semiurgent surgical procedures involve multiple patient- and procedure-related factors, making it difficult to develop standardized management protocols, unlike for elective surgery.[74,75] Consequently, there is wide variability in management practices for DOAC-treated patients undergoing an emergent or urgent surgical procedure.[71,76]

A proposed empirical approach, which has not been assessed in randomized clinical trials, is shown in Figure 2. This management approach is based on whether medical centers can provide DOAC level testing, which includes DOAC-specific assays to measure the anticoagulant effect of apixaban, edoxaban, and rivaroxaban (expressed in anti–factor Xa level, ng/mL) and the dilute thrombin time or ecarin clotting time to measure the anticoagulant effect of dabigatran (expressed in seconds). DOAC level testing has a rapid turnaround time (<30 minutes) but is not available in many medical centers in the US, especially for the oral direct factor Xa inhibitors.

Emergent Surgical Procedures

If DOAC level testing is available, a DOAC level at or above 50 ng/mL may necessitate use of a DOAC reversal agent, whereas a level less than 50 ng/mL may allow the operation to proceed without a reversal intervention. However, no high-quality evidence is available to support this guideline. For patients who require an urgent surgical procedure at a medical center that does not perform DOAC level testing, DOAC reversal medication should be considered if the most recent DOAC dose was taken less than 48 hours before the procedure.

Urgent or Semiurgent Surgical or Nonsurgical Procedures

Patients who require an urgent surgical procedure and have a DOAC level less than 50 ng/mL may proceed to surgery without use of a DOAC reversal agent. For patients with a DOAC level more than 50 ng/mL, testing can be repeated closer to the operation and if less than 50 ng/mL, administration of a reversal agent is not needed. Patients with DOAC level more than 50 ng/mL upon retesting should be considered for treatment with a reversal agent. For patients requiring an urgent operation at a medical center where DOAC level testing is not available, DOAC reversal medication should be considered if the most recent DOAC dose was taken less than 48 hours before the operation. Semiurgent surgical procedures should be delayed until at least 48 hours has elapsed since the last dose of DOAC.

Perioperative DOAC Management Issues Needing Further Study

An ongoing randomized trial (PAUSE-2) is enrolling patients with atrial fibrillation taking DOACs who require elective surgical procedures involving neuraxial anesthesia to evaluate the appropriate length of DOAC interruption. An open-label, randomized, prospective, multicenter study (ANNEXA-RS) is planning to enroll patients requiring an urgent operation or procedure within 15 hours of most recent dose of a factor Xa inhibitor DOAC to compare andexanet-α with usual care. There are preliminary published data about DOAC point-of-care whole blood and urine assays,[77-79] but well-designed clinical management studies are needed.

Limitations

This review has several limitations. First, many of the recommended practices for perioperative DOAC management are based on limited evidence, especially for emergent or urgent surgical procedures. Second, some relevant studies may have been missed. Third, a formal quality assessment of the included literature was not performed.

Conclusions

When patients who are taking a DOAC require an elective surgical or nonsurgical procedure, standardized management protocols can be applied that do not require testing DOAC levels or heparin

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bridging. When patients taking a DOAC require an emergent, urgent, or semiurgent surgical procedure, anticoagulant reversal agents may be appropriate when DOAC levels are elevated or not available.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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