NOACS/DOACS*: PERIOPERATIVE MANAGEMENT

Thrombosis Canada
Thrombose Canada

*NOACs/DOACs = Non-vitamin K antagonist Oral Anticoagulants, also known as Direct Oral Anticoagulants

OBJECTIVE:

To provide guidance for the perioperative management of patients who are receiving a direct oral anticoagulant (DOAC) and require an elective surgery/procedure.

For guidance on management of patients who require an urgent or emergency surgery/procedure, please refer to the Perioperative Anticoagulant Management Algorithm found on the Thrombosis Canada website under the "Tools" tab.

BACKGROUND:

Four DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) are approved for clinical use in Canada based on findings from large randomized trials.

The perioperative management of DOAC-treated patients aims to minimize thromboembolic risk while interrupting anticoagulant therapy (if necessary) so there is no (or minimal) residual anticoagulant effect at the time of surgery, and to ensure timely but careful resumption after surgery so as to not incur an increased risk for post-operative bleeding.

There are 3 important considerations for perioperative management of patients taking a DOAC:

1) Reliable laboratory tests to confirm the absence of a residual anticoagulant effect of DOACs are not widely available.
2) Half-lives of DOACs differ and increase with worsening renal function, affecting when the drug should be stopped before surgery.
3) DOACs have rapid onset of action, with a peak anticoagulant effect occurring 1-2 hours after oral intake.

In the absence of laboratory tests to reliably measure their anticoagulant effect, the perioperative administration of DOACs should be influenced by:

1) Drug elimination half-life (with normal renal function),
2) Effect of renal function on drug elimination half-life
3) Bleeding risk associated with the type of surgery/procedure and anesthesia (specifically neuraxial blockade) (**Table 1**)

EVIDENCE SUPPORTING PERIOPERATIVE MANAGEMENT OF PATIENTS TAKING A DOAC:

There are emerging data relating to the efficacy and safety of the proposed perioperative management of DOAC-treated patients. The PAUSE study was the first study to assess a standardized perioperative management strategy in patients who were receiving a DOAC and required DOAC interruption prior to an elective (planned) surgery/procedure. In this study of 3,007 DOAC-treated patients with atrial fibrillation, a simple perioperative DOAC management that did not involve perioperative heparin bridging or preoperative coagulation function testing was associated with low rates of major bleeding (<2%) and stroke/systemic embolism (<1%).

PERIOPERATIVE MANAGEMENT (BASED ON PAUSE PROTOCOL):

Patients Receiving Dabigatran

Pre-Operative Management (Table 2):

- **MINIMAL-BLEED-RISK procedure:** In patients who require a minor dental procedure, cataract procedure, or minor skin procedure it is likely safe not to interrupt anticoagulation (as is done in warfarin-treated patients) but data to support such practice is lacking. An alternative approach would be to hold dabigatran on the day of the procedure or, if dabigatran is not interrupted, to delay that day's dose for 4-6 hours after the procedure.
- **LOW/MODERATE-BLEED-RISK surgery/procedures:** For patients with normal renal function or mild impairment, last dose of dabigatran 2 days before the surgery/procedure (i.e. skip 2 doses before a surgery/procedure), which corresponds to approximately 2-3 half-lives elapsed between stopping dabigatran and surgery. There may be a 12-25% anticoagulant effect at the time of surgery, which is acceptable for these procedures.
- **HIGH-BLEED-RISK (includes any neuraxial [i.e. spinal or epidural] anesthesia or procedure)**: Depending on renal function, last dose of dabigatran 3 to 5 days before surgery/procedure (i.e. skip 4 to 8 doses), which corresponds to approximately 4-5 half-lives elapsed between stopping dabigatran and surgery. This ensures minimal (3-6%) residual anticoagulant effect at the time of surgery and allows patients to have spinal anesthesia or high bleeding risk surgery (e.g. intracranial or cardiac).
- If renal function is moderately impaired (CrCl 30-49 mL/min), 1-2 additional days of interruption is required to ensure elimination of any residual anticoagulant effect, as 80% of dabigatran is cleared by the kidneys.

Post-Operative Management (Table 3):

Resumption of dabigatran 150 mg or 110 mg twice daily should be done cautiously after major surgery or in patients at increased bleeding risk, as this is a therapeutic-dose which is higher than that used for post-operative VTE prevention.

Patients Receiving Rivaroxaban

Pre-Operative Management (Table 2):

- **MINIMAL-BLEED-RISK procedure**: In patients who require a minor dental procedure, cataract procedure, or minor skin procedure it is likely safe not to interrupt anticoagulation (as is done

in warfarin-treated patients) but data to support such practice is lacking. An alternative approach would be to hold rivaroxaban on the day of the procedure or, if rivaroxaban is not interrupted, to delay that day's dose for 4-6 hours after the procedure.

- **LOW/MODERATE-BLEED-RISK surgery/procedure:** Last dose of rivaroxaban 2 days before surgery/procedure (i.e. skip 1 dose), which corresponds to approximately 2-3 half-lives elapsed between stopping rivaroxaban and surgery.
- **HIGH-BLEED-RISK surgery/procedure (includes any neuraxial [i.e., spinal or epidural] anesthesia or procedure)**: Last dose of rivaroxaban 3 days before surgery/procedure (i.e. skip 2 doses), which corresponds to approximately 4-5 half-lives elapsed between stopping rivaroxaban and surgery.

Post-Operative Management (Table 3):

Resumption of rivaroxaban 20 mg (or 15 mg if usual dose) once daily should be done cautiously after major surgery or in patients at increased bleeding risk, as this is a therapeutic-dose which is higher than that used for post-operative VTE prevention.

Patients Receiving Apixaban

Pre-Operative Management (Table 2):

- **MINIMAL-BLEED-RISK procedure:** In patients who require a minor dental procedure, cataract procedure, or minor skin procedure it is likely safe not to interrupt anticoagulation (as is done in warfarin-treated patients) but data to support such practice is lacking. An alternative approach would be to hold apixaban on the day of the procedure or, if apixaban is not interrupted, to delay that day's dose for 4-6 hours after the procedure.
- **LOW/MODERATE-BLEED-RISK surgery/procedure**: Last dose of apixaban 2 days before surgery/procedure (i.e. skip 2 doses), which corresponds to approximately 2-3 half-lives elapsed between stopping apixaban and surgery.
- **HIGH-BLEED-RISK surgery/procedure (includes any neuraxial [i.e., spinal or epidural] anesthesia or procedure)**: Last dose of apixaban 3 days before surgery/procedure (i.e. skip 4 doses), which corresponds to approximately 4-5 half-lives elapsed between stopping apixaban and surgery.

Post-Operative Management (Table 3):

Resumption of apixaban 5 mg twice daily should be done cautiously after major surgery or in patients at increased bleeding risk, as this is a therapeutic-dose which is higher than that for post-operative VTE prevention.

Patients Receiving Edoxaban

Pre-Operative Management (Table 2):

- **MINIMAL-BLEED-RISK procedure:** In patients who require a minor dental procedure, cataract procedure, or minor skin procedure it is likely safe not to interrupt anticoagulation (as is done in warfarin-treated patients) but data to support such practice is lacking. An alternative approach would be to hold edoxaban on the day of the procedure or, if edoxaban is not interrupted, to delay that day's dose for 4-6 hours after the procedure.

- **LOW/MODERATE-BLEED-RISK surgery/procedure:** Last dose of edoxaban 2 days before surgery/procedure (i.e. skip 1 dose), which corresponds to approximately 2-3 half-lives elapsed between stopping edoxaban and surgery.
- **HIGH-BLEED-RISK surgery/procedure (includes any neuraxial [i.e., spinal or epidural] anesthesia or procedure)**: Last dose of edoxaban 3 days before surgery/procedure (i.e. skip 2 doses), which corresponds to approximately 4-5 half-lives elapsed between stopping edoxaban and surgery.

Post-Operative Management (Table 3):

Resumption of edoxaban 60 mg or 30 mg daily should be done cautiously after major surgery or in patients at increased bleeding risk, as this is a therapeutic-dose.

TABLE 1: BLEEDING RISK FOR VARIOUS INVASIVE/SURGICAL PROCEDURES

MINIMAL-BLEED-RISK	LOW/MODERATE-BLEED-RISK	HIGH-BLEED-RISK
• Cataract surgery • Dermatologic procedures (e.g. biopsy) • Gastroscopy or colonoscopy *without biopsies* • Coronary angiography (using radial arterial approach) • Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used) • Selected procedures with small-bore needles (e.g. thoracentesis, paracentesis, arthrocentesis) • Dental extractions (1 or 2 teeth) • Endodontic (root canal) procedure • Subgingival scaling or other cleaning	• Abdominal surgery (e.g. cholecystectomy, hernia repair, colon resection) • Other general surgery (e.g. breast) • Other intrathoracic surgery • Other orthopedic surgery • Other vascular surgery • Non-cataract ophthalmologic surgery • Coronary angiography (using femoral artery approach) • Gastroscopy or colonoscopy *with* biopsies • Selected procedures with large-bore needles (e.g. bone marrow biopsy, lymph node biopsy) • Complex dental procedure (e.g. multiple tooth extractions)	• Any surgery or procedure with neuraxial (spinal or epidural) anesthesia • Neurosurgery (intracranial or spinal) • Cardiac surgery (e.g. CABG, heart valve replacement) • Major vascular surgery (e.g. aortic aneurysm repair, aortofemoral bypass) • Major orthopedic surgery (e.g. hip/knee joint replacement surgery) • Lung resection surgery • Urological surgery (e.g. prostatectomy, bladder tumour resection) • Extensive cancer surgery (e.g. pancreas, liver) • Intestinal anastomosis surgery • Reconstructive plastic surgery • Selected procedures involving vascular organs (e.g. kidney biopsy, prostate biopsy) or high bleed risk intervention (e.g. pericardiocentesis, spinal injection, polypectomy)

TABLE 2: SUGGESTED PRE-OPERATIVE MANAGEMENT OF PATIENTS TAKING A DOAC

Drug (dose regimen)	Renal function	Low/moderate-bleed-risk surgery/procedure* *12-25% residual anticoagulant effect at time of surgery acceptable*	High-Bleed-Risk surgery/procedure including neuraxial procedures*† *<10% residual anticoagulant effect at time of surgery acceptable*
Dabigatran (twice daily)			
	Normal renal function or mild impairment (CrCl ≥50 mL/min) $t_{1/2}$ 7-17 hours	Give last dose 2 days before surgery/procedure (i.e. skip 2 doses)	Give last dose 3 days before surgery/procedure (i.e. skip 4 doses)
	Moderate renal impairment (CrCl 30-49 mL/min) $t_{1/2}$ 17-20 hours	Give last dose 3 days before surgery/ procedure (i.e. skip 4 doses)	Give last dose 5 days before surgery/procedure (i.e. skip 8 doses)
Rivaroxaban (once daily)			
	Normal renal function, mild or moderate impairment (CrCl ≥30 mL/min) $t_{1/2}$ 7-11 hours	Give last dose 2 days before surgery/procedure (i.e. skip 1 dose)	Give last dose 3 days before surgery/procedure (i.e. skip 2 doses)
Apixaban (twice daily)			
	Normal renal function, mild or moderate impairment (CrCl ≥30 mL/min) $t_{1/2}$ 8-12 hours	Give last dose 2 days before surgery/procedure (i.e. skip 2 doses)	Give last dose 3 days before surgery/procedure (i.e. skip 4 doses)
Edoxaban (once daily)			
	Normal renal function, mild or moderate impairment (CrCl ≥30 mL/min) $t_{1/2}$ 10-14 hours	Give last dose 2 days before surgery/procedure (i.e. skip 1 dose)	Give last dose 3 days before surgery/procedure (i.e. skip 2 doses)

*No anticoagulant taken on the day of surgery/procedure. †Comprise spinal/epidural anesthesia and spinal/epidural injections/procedures.

TABLE 3. SUGGESTED GUIDE FOR *POST-OPERATIVE* MANAGEMENT OF PATIENTS RECEIVING A DOAC

DRUG	LOW/MODERATE-BLEED-RISK SURGERY/PROCEDURE	HIGH-BLEED-RISK SURGERY/PROCEDURE
Dabigatran	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
Rivaroxaban	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
Apixaban	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
Edoxaban	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim

SPECIAL CONSIDERATIONS:

Patients with Impaired Renal Function:

An approach to managing patients with mild-to-moderate renal dysfunction is shown in **Table 2,** but for patients with severe renal dysfunction (CrCl <30 mL/min) who are generally ineligible for DOACs, perioperative management is unclear.

Need for Bridging in DOAC-treated Patients:

In general, the rapid offset and onset of action of DOACs obviates the need for 'heparin bridging' as is done in selected warfarin-treated patients.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- Edoxaban (Lixiana®)
- NOACs/DOACs: Coagulation Tests
- NOACs/DOACs: Comparison and Frequently Asked Questions
- Rivaroxaban (Xarelto®)

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Date of Version: 15May2020

Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the