



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 interrupt 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 (**Table 1**)
- 4) Whether patient is to receive spinal/epidural anesthesia

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. In RELY, a trial comparing dabigatran (150 mg or 110 mg)

with warfarin for stroke prevention in atrial fibrillation, there were >4,500 patients who had anticoagulant interruption for a surgery/procedure. The incidence of perioperative bleeding was similar in dabigatran- and warfarin-treated patients, suggesting that dabigatran-treated patients can be safely managed perioperatively. Similar findings have been observed for the perioperative management of apixaban-treated, edoxaban-treated and rivaroxaban-treated patients.

PERIOPERATIVE MANAGEMENT:

Patients Receiving Dabigatran

Pre-Operative Management (Table 2):

- **Minor surgery/procedure (LOW BLEEDING RISK):** 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.
- **MODERATE BLEEDING RISK Procedures:** Stop dabigatran 1 day before 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.
- **Major surgery/procedure including neuraxial anesthesia (HIGH BLEEDING RISK):** Depending on renal function, stop dabigatran 2 or 4 days before surgery (i.e. skip 4 or 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):

- **Minor surgery/procedure (LOW BLEEDING RISK):** 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.

- **MODERATE BLEEDING RISK procedure:** Stop rivaroxaban 1 day before surgery/procedure (i.e. skip 1 dose), which corresponds to approximately 2-3 half-lives elapsed between stopping rivaroxaban and surgery.
- **Major surgery/procedure including neuraxial anesthesia (HIGH BLEEDING RISK):** Stop rivaroxaban 2 days before surgery (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):

- **Minor surgery/procedure (LOW BLEEDING RISK):** 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.
- **MODERATE BLEEDING RISK procedure:** Stop apixaban 1 day before surgery/procedure (i.e. skip 2 doses), which corresponds to approximately 2-3 half-lives elapsed between stopping apixaban and surgery.
- **Major surgery/procedure including neuraxial anesthesia (HIGH BLEEDING RISK):** Stop apixaban 2 days before surgery (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):

- **Minor surgery/procedure (LOW BLEEDING RISK):** 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.
- **MODERATE BLEEDING RISK procedure:** Stop edoxaban 1 day before surgery/procedure (i.e. skip 1 dose), which corresponds to approximately 2-3 half-lives elapsed between stopping edoxaban and surgery.

- **Major surgery/procedure including neuraxial anesthesia (HIGH BLEEDING RISK):** Stop edoxaban 2 days before surgery (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

LOW/VERY LOW RISK	MODERATE RISK	HIGH RISK
<ul style="list-style-type: none"> • Dental extractions (1 or 2 teeth), endodontic (root canal) procedure, • Subgingival scaling or other cleaning • Cataract surgery • Dermatologic procedures (e.g. biopsy) • Gastroscopy or colonoscopy without biopsies • Coronary angiography • Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used) • Selected procedures (e.g. thoracentesis, paracentesis, arthrocentesis) 	<ul style="list-style-type: none"> • Other intra-abdominal surgery (e.g. laparoscopic cholecystectomy, hernia repair, colon resection) • Other general surgery (e.g. breast) • Other intrathoracic surgery • Other orthopedic surgery • Other vascular surgery • Non-cataract ophthalmologic surgery • Gastroscopy or colonoscopy with biopsies • Selected procedures (e.g. bone marrow biopsy, lymph node biopsy) • Complex dental procedure (e.g. multiple tooth extractions) 	<ul style="list-style-type: none"> • Any surgery or procedure with neuraxial (spinal or epidural) anesthesia • Neurosurgery (intracranial or spinal) • Cardiac surgery (e.g. CABG, heart valve replacement) • Major intra-abdominal surgery (e.g. intestinal anastomosis) • Major vascular surgery (e.g. aortic aneurysm repair, aortofemoral bypass) • Major orthopedic surgery (e.g. hip or knee replacement) • Lung resection surgery • Urological surgery (e.g. prostatectomy, bladder tumour resection) • Extensive cancer surgery (e.g. pancreas, liver) • Reconstructive plastic surgery • Selected procedures (e.g. kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)

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

DRUG (DOSE REGIMEN)	RENAL FUNCTION	MODERATE BLEEDING RISK SURGERY/PROCEDURE* <i>12-25% residual anticoagulant effect at time of surgery acceptable</i>	MAJOR SURGERY/PROCEDURE INCLUDING NEURAXIAL PROCEDURES*† (HIGH BLEEDING RISK) <i><10% residual anticoagulant effect at time of surgery acceptable</i>
Dabigatran (twice daily)	Normal renal function or mild impairment (CrCl \geq 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 \geq 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)
	Normal renal function, mild or moderate impairment (CrCl \geq 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 \geq 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. †Neuraxial procedures include spinal anesthesia, epidural catheter insertion and epidural catheter removal.

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

DRUG	MODERATE BLEEDING RISK SURGERY/PROCEDURE	MAJOR SURGERY/PROCEDURE
	(MODERATE BLEEDING RISK)	(HIGH BLEEDING RISK)
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 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.

Pediatrics:

There are no studies evaluating the use of DOACs in children, although studies are underway. DOACs in children are not recommended until dosing, safety and efficacy are confirmed.

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: 2019Apr30

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