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Direct Oral Anticoagulants (DOACs)

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Scope

This guideline provides recommendations on the use of direct oral anticoagulants (DOACs) in adults aged ≥19 years for the following indications:

- prevention of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF);
- treatment of hemodynamically stable venous thromboembolism (VTE); and,
- prevention of arterial vascular events in patients with stable coronary artery disease with or without peripheral artery disease.

How to make the decision to use a DOAC (instead of another anticoagulant), periprocedural management, and emergency reversal are all outside the scope of this guideline. Refer to *BC Guidelines: Warfarin* and *BC Guidelines: Oral Anticoagulants: Elective Interruption & Emergency Reversal* for more information on these topics.

Key Recommendations

- DOACs are considered **first-line** therapy for:
  - prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) for whom anticoagulation is indicated; and
  - treatment of hemodynamically stable venous thromboembolism (VTE).
- Do not use DOACs (instead of warfarin) for anticoagulation in mechanical heart valves, AF with moderate to severe mitral stenosis, and other very high-risk thrombotic indications.
- Confirm appropriate dosing as this varies widely across different indications. Dose adjustments may be indicated for renal impairment, age, weight, and drug-drug interactions. Refer to *Table 2: DOAC dosing and therapeutic considerations based on indication* and *Appendix A: DOAC Drug Interactions* for more information.
- Check renal function for **all** patients and liver function in patients with known hepatic dysfunction prior to initiating a DOAC. Monitor one or both periodically, based on clinical status.
- DOACs **do not** require routine laboratory monitoring. International normalized ratio (INR) and activated partial thromboplastin clotting time (aPTT) values do not reflect anticoagulant level or activity and should not be used to detect or exclude the presence of a DOAC.
- Check for potential drug-drug interactions and consider alternative therapy if a significant interaction is present.

Definition

DOACs are a class of drugs with potent anticoagulant effects. DOACs work by inhibiting key activated clotting factors in the coagulation cascade. There are four DOACs currently available in Canada: three activated factor X (FXa) inhibitors (apixaban, edoxaban, and rivaroxaban) and one direct thrombin inhibitor (dabigatran).

Pharmacological Properties

While DOACs have similar properties, their safety and suitability for individual patients differ based on each drug's pharmacological profile.[1,2] As a class, DOACs have relatively predictable pharmacokinetic and pharmacodynamic properties, including:

- Rapid onset of action, reaching therapeutic effect in less than 4 hours.
- Half-lives that are highly dependent on renal and/or liver function.

DOACs have fewer food and drug interactions as compared to warfarin.[3] However there are many drugs that should **not** be used concomitantly with DOACs. Refer to *Table 2: DOAC dosing and therapeutic considerations based on indication* and *Appendix A: DOAC Drug Interactions* for more information on therapeutic considerations and drug-drug interactions.

Therapeutic Indications

DOACs are approved in three major clinical settings where oral anticoagulation is commonly used, but are not preferred over warfarin for certain patient populations and are contraindicated for others (see the *Initiating a DOAC* section below for more information). Refer to *Table 2: DOAC dosing and therapeutic considerations based on indication* for more detail on DOAC dosing and therapeutic considerations based on indication and the *Resources* section for information on the Rapid Access to Consultative Expertise (RACE) program.

DOACs for Non-valvular Atrial Fibrillation (NVAF)

DOACs are considered first line treatment for most patients with NVAF (strong recommendation, high-quality evidence),[4,5] based on direct comparison with warfarin in robust clinical trials investigating the prevention of stroke and systemic embolism in patients with NVAF.[6–9] As a class, DOACs have been shown to be superior or non-inferior to warfarin in terms of efficacy,[10,11] with reduced risk of stroke, intracranial bleeding, and all-cause mortality.[10] DOACs also have comparable or better safety profiles, with no difference in major bleeding and a lower risk of intracranial bleeding.[10] DOACs also offer important practical benefits for patients and providers (e.g., ease of administration, fewer dietary interactions, reduced monitoring requirements).

DOACs for Venous Thromboembolism (VTE)

DOACs are considered first line treatment for acute VTE and prevention of recurrent VTE in most patients because of their overall safety profile and convenience when compared to warfarin.[12–14] However, there is no difference in all-cause mortality, recurrent thrombosis or major bleeding between the use of DOACs and warfarin for VTE.[14] Anticoagulant therapy for acute VTE is recommended for at least three months.[15] Extended DOAC use in select patients (e.g., unprovoked index event or ongoing risk factors) beyond six months can reduce VTE recurrence and/or death when compared to a placebo,[16] but it is associated with a higher risk of non-major clinically important bleeding.[16]

DOACs for Coronary Artery Disease (CAD) and Peripheral Artery Disease (PAD)

A very low dose of rivaroxaban (2.5 mg twice daily) combined with low-dose ASA once daily reduces the risk of cardiovascular death, stroke or myocardial infarction in patients with stable CAD and/or PAD.[17,18] Recent data show that this combination is also effective in reducing major adverse limb and cardiovascular thrombotic events after endovascular intervention in patients with PAD; these outcomes include limb ischemia, amputation, myocardial infarction, ischemic stroke, and death.[19] However, the combination of very low dose rivaroxaban and low-dose ASA (dual pathway inhibition) is associated with an increased risk of major bleeding (primarily in the gastrointestinal tract) when compared to ASA alone, although no significant increase in fatal/critical bleeding has been observed.[17,20]

Initiating a DOAC

Clinical Assessment

Before initiating a DOAC, ensure that the patient does not have a contraindication where warfarin or low molecular weight heparin (LMWH) is recommended instead. Refer to *Table 1: Absolute contraindications for DOACs* for more information on DOAC contraindications and *BC Guidelines: Warfarin* for more general warfarin information. Of note, DOACs are **not** contraindicated in frail elderly populations; a risk-benefit analysis favours anticoagulation for patients with NVAF in this population.[21]

Table 1: Absolute contraindications for DOACs

Absolute Contraindication	Alternative Recommendation
Mechanical heart valve	Warfarin[22]
Atrial fibrillation with moderate to severe mitral stenosis	Warfarin[4]
Pregnancy	LMWH, especially during first trimester
Breastfeeding	LMWH or warfarin
Triple positive antiphospholipid syndrome[23]	Refer to specialist for alternative management
Severe thrombocytopenia (platelet count < 50 x 109/L)	Refer to specialist for alternative management
Clinically significant drug-drug interactions	Refer to *Table 2: DOAC dosing and therapeutic considerations based on indication* and *Appendix A: DOAC Drug Interactions*

Abbreviations: LMWH = low molecular weight heparin.

Specialty consultation is also recommended for certain patients where the evidence is weak or for patients at increased risk of adverse outcomes, including but not limited to:

- Severe kidney dysfunction (e.g., CrCl < 30 mL/min);
- Liver impairment (e.g., *Child-Pugh Score* class B or C, depending on specific DOAC);
- Active cancer;
- Extremes of bodyweight (e.g, body weight <40 or >120 kg; BMI ≤18.5 or ≥35 kg/m^2);[24]
- Post bariatric or extensive bowel surgery;
- Solid organ or stem cell transplant; and/or
- Human immunodeficiency virus (HIV). Refer to *Table 2: DOAC dosing and therapeutic considerations based on indication* for more detail on DOAC dosing and therapeutic considerations and a *HIV drug checker* for more information.

Consult with your local pharmacist regarding potential drug-drug interactions that may reduce DOAC efficacy or increase a patient's risk of bleeding. Consider alternative therapy if any significant interaction is present. Of note, polypharmacy in elderly patients may increase risks of adverse outcomes from drug-drug interactions. Refer to *Table 2: DOAC dosing and therapeutic considerations based on indication* for more details on DOAC dosing and therapeutic considerations and *Appendix A: DOAC Drug Interactions* for more information on drug interactions.

Laboratory Testing

Complete blood count (CBC) and Creatinine Clearance (CrCl) must be checked for all patients prior to initiating a DOAC. The CrCl (calculated using *Cockcroft-Gault formula*) should be used to determine DOAC dosage according to the patient's age, weight, and serum creatinine.[25] Do not use the estimated glomerular filtration rate (eGFR) provided by laboratory reports as this can lead to inappropriate DOAC dosing in a significant proportion of patients. Liver function should also be checked in those with known hepatic dysfunction (e.g., cirrhosis, hepatitis) before starting a DOAC.

Patient Education

Patient education is an important component of drug initiation. Given that DOAC half-lives are relatively short (~12 hours), missing 1-2 doses can lead to subtherapeutic coverage and thus increased risk of stroke or recurrent thrombosis. Twice-daily DOACs (e.g., apixaban) may be more appropriate than once-daily DOACs (e.g., rivaroxaban) for patients for whom adherence is a concern.[26]

Indication, Duration, Risks and Benefits

- Reason for DOAC therapy
- Duration of therapy
- Reduction in stroke and thrombosis
- Increased risk of bleeding

Patient's Responsibilities

- Take DOAC as instructed (e.g. rivaroxaban needs to be taken with food)
- Avoid missing doses
- Avoid large amounts of alcohol, grapefruit or cranberry juice, and herbal supplements

Safe Practices for Patients

- Use a daily pill box or dosette to keep track of doses
- Wear a MedicAlert bracelet or equivalent
- Use effective contraception (if relevant)
- Go to the Emergency Department if signs of stroke, clotting or serious bleeding

Dosage

The table below is not an exhaustive list of all contraindications, precautions, and drug interactions. Consult a *drug interaction checker* or pharmacist, as needed. Refer to the *Resources* section for *Child-Pugh Score* and *Cockcroft-Gault* calculators.

Table 2: DOAC dosing and therapeutic considerations based on indication

Name/Cost	Dose in NVAF	Dose in VTE	Dose in CAD/PAD	Therapeutic Considerations

Apixaban
ELIQUIS, generics
Tabs: 2.5, 5 mg
 	
PharmaCare regular benefit[a]
~$30/month[b]
	5 mg BID
	OR
	2.5 mg BID if ≥ 2 of the following:
	• age ≥ 80 years
	• weight ≤ 60 kg
	• Serum creatinine ≥ 133 µmol/L
		Acute: 10 mg BID x 7 days then 5 mg BID x 3 to 6 months
		
		Chronic (> 6 months): 2.5 or 5 mg BID
			Not indicated	• Contraindicated/avoid use:
				• CrCl < 15 mL/min, Child-Pugh class C
				  • (↑ bleed risk): azole-antimycotics (e.g., ketoconazole), cobicistatc, HIV protease inhibitors (e.g., ritonavir)
				  • (↑ thromboembolic risk): carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort
				• Discuss with specialist for CrCl 15 to 29 mL/min

Rivaroxaban
XARELTO, generics
Tabs: 2.5, 10, 15, 20 mg
 	
Oral suspension: 1 mg/mL
 	
PharmaCare regular benefit (tablets only)[a]
~$25/month[b]
	20 mg daily with food
	OR
	15 mg daily with food if CrCl 30 to 49 mL/min
		Acute: 15 mg BID with food x 21 days then 20 mg daily with food x 3 to 6 months
		
		Chronic (> 6 months): 20 mg daily with food or 10 mg daily
			2.5 mg BID with ASA 81 mg daily	• Contraindicated/avoid use:
				  • CrCl < 15 mL/min, Child-Pugh class B and C
				  • (↑ bleed risk): azole-antimycotics (e.g., ketoconazole), cobicistat, dronedarone, HIV protease inhibitors (e.g., ritonavir)[d]
				  • (↑ thromboembolic risk): carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort[c], post-gastrectomy (highly absorbed in stomach)
				  • Data limited for CrCl 15 to 30 mL/min
				• Take 15 mg and 20 mg doses with food to facilitate adequate absorption

Dabigatran
PRADAXA, generics
Caps: 75, 110, 150 mg
 	
PharmaCare limited coverage benefit for NVAF only[a]
~$85/month[b]
	150 mg BID
	OR
	110 mg BID if any of the following:
	• age ≥ 80 years
	• higher risk of bleeding, including age ≥ 75 years with ≥ 1 risk factor for bleeding (refer to *product monograph*)
		Acute: LMWH x 5 to 10 days followed by 150 mg BID (or 110 mg BID) x 3 to 6 months
		
		Chronic (> 6 months): 150 mg or 110 mg BID
			Not indicated	• Contraindicated/avoid use:
				  • CrCl < 30 mL/min, Child-Pugh class C
				  • (↑ bleed risk): azole-antimycotics (e.g., ketoconazole), dronedarone, glecaprevir/pibrentasvir (Maviret™), verapamil, clarithromycinc, erythromycin
				  • (↑ thromboembolic risk): carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort
				• Increased gastric pH may ↓ absorption (antacids, PPIs)
				• Take with food to reduce dyspepsia
				• Must be stored in original packaging

Edoxaban
LIXIANA
Tabs: 15, 30, 60 mg
 	
Pharmacare non-benefit[a]
~$100/month[b]
	60 mg daily
	OR
	30 mg daily if any of the following:
	• CrCl 15 to 50 mL/min
	• weight ≤ 60 kg
	• concomitant P-gp inhibitors (see Therapeutic Considerations)
		Acute: LMWH x 5 to 10 days followed by 60 mg daily (or 30 mg daily) x 3 to 6 months
		
		Chronic (> 6 months): 60 mg or 30 mg daily
			2.5 mg BID with ASA 81 mg daily	• Contraindicated/avoid use:
				  • CrCl < 15 mL/min, Child-Pugh class C
				  • (↑ thromboembolic risk): carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort[c]
				• Reduce dose (30 mg daily) with: cyclosporine, dronedarone, clarithromycin[c], erythromycin, ketoconazole, quinidine (↑ bleed risk)

Abbreviations: BID = twice daily; caps = capsules; CrCl = creatinine clearance; kg = kilogram; LMWH = low molecular weight heparin; µmol/L = micromoles per litre; mg = milligrams; mL/min = milliliters per minute; P-gp = P-glycoprotein; tabs = tablets; ↑ = increase; ↓ = decrease.

Footnotes:

a) PharmaCare coverage as of December 2023 (subject to revision). Limited Coverage: Requires Special Authority to be eligible for reimbursement*. Non-benefit: Not eligible for reimbursement. *Reimbursement is subject to the rules of a patient's PharmaCare plan, including any deductibles. In all cases, coverage is subject to drug price limits set by PharmaCare. See: *www.health.gov.bc.ca/pharmacare/plans/index.html* and *www.health.gov.bc.ca/pharmacare/policy.html* for further information. See: *https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/special-authority/sa-drug-list* for Special Authorization Form for dabigatran;

b) Drugs costs are the BC retail cost rounded up to the nearest $5 of the generic, when available from *mckesson.ca*. Current as of December 2023 and does not include retail markups or pharmacy fees;

c) Lexicomp Drug Interactions. Accessed online May 5, 2022 from *https://www.uptodate.com/drug-interactions/*;

d) HIV Drug Interactions. University of Liverpool. Accessed online May 5, 2022 from *https://www.hiv-druginteractions.org/checker*

Switching Between Warfarin and a DOAC

There is no need to switch to a DOAC for patients who are currently and successfully anticoagulated with warfarin. Changes in anticoagulant therapy are associated with a transient increased risk of stroke and systemic embolism. However, switching may be indicated for patients who are frequently outside the therapeutic INR range or those who cannot adhere to regular laboratory monitoring.[28] Refer to *Appendix B: Switching Between Warfarin and DOAC* for recommended approaches to switching between anticoagulant therapies.

Ongoing Management

Clinical Follow-Up

Reassess patients within 1-2 months of DOAC initiation to assess adherence, review potential adverse events (e.g., gastrointestinal upset, excessive bruising, bleeding), and assess bleed risk. Frequency of follow-up thereafter is individualized based on clinical factors:[4,29]

- annually for those with normal renal function,
- every six months for those with eGFR 30-60 mL/min, and
- quarterly for those with eGFR < 30 mL/min.

At follow-up, confirm ongoing indication for DOAC use, review current medications for drug-drug interactions, assess patient's relative risks of bleeding and/or thromboembolism, and address any adverse events. Periodically educate patients regarding the importance of medication adherence and early identification of adverse events, including signs of stroke and recurrent thrombosis.

Laboratory Testing

Poor renal function is a risk factor for bleeding and thus all patients on a DOAC should be tested at least once every 6-12 months.[29,30] More frequent renal function testing may be indicated for certain patients (e.g., elderly patients with borderline renal function).[29]

Since all DOACs are partially metabolized by the liver[31] and liver impairment can increase the risk of bleeding, liver function monitoring should be considered every 6-12 months for patients who have known hepatic dysfunction.[26]

Unlike warfarin, DOACs do not require routine laboratory monitoring of the anticoagulant effect. Classic coagulation tests like INR and partial thromboplastin time (PTT) are not helpful for assessing anticoagulant activity because results may be normal or abnormal, and prolongation of these clotting times do not reflect the degree of anticoagulant activity present.[26] Consult a specialist if measuring the anticoagulant effect of a DOAC is being considered under special circumstances (e.g. after bariatric surgery). Refer to the *Resources* section below for information on the RACE line.

DOACs can interfere with special coagulation tests. Do not perform thrombophilia testing while a patient is taking a DOAC. If special coagulation tests are being considered, contact a specialist. Refer to the *Resources* section below for information on the RACE line.

Bleeding Complications

Bleeding is a common adverse event for all anticoagulant drugs.[32,33] The risk of bleeding is influenced by the concomitant use of certain medications, patient co-morbidities, and lifestyle. Refer to *Table 3: Risk factors for bleeding complications on anticoagulation therapy* for risk factors for bleeding complications on anticoagulation therapy.

Table 3: Risk factors for bleeding complications on anticoagulation therapy[34–36]

Risk Factor Category	Specific Risk Factors
Age	> 70 years
Time Period	Within 3 months of starting treatment
Cardiac	Uncontrolled hypertension (> 160/100 mmHg), heart failure
Gastrointestinal	History of gastrointestinal hemorrhage, active peptic ulcer, hepatic insufficiency
Hematologic/Oncologic	Thrombocytopenia, platelet dysfunction, coagulation defect, malignancy
Neurologic	History of stroke, cognitive or psychological impairment
Renal	Renal insufficiency (eGFR < 60 mL/min)
Trauma	Recent trauma
Alcohol	Excessive alcohol intake
Medications	Use of ASA or NSAIDs. See *Appendix A: DOAC Drug Interactions* for more information on drug interactions.

Abbreviations: ASA = acetylsalicylic acid; INR = international normalized ratio; mmHg = millimetres of mercury, mL = millilitre; NSAIDs = nonsteroidal anti-inflammatory drugs.
Adapted from: Warfarin Reversal Position Statement, Australasian Society of Thrombosis & Haematosis[37]

When a patient on a DOAC is bleeding, the decision to continue, temporarily interrupt or permanently stop the DOAC depends on the severity of the bleeding event, the likelihood the event can be stopped with minimal intervention, and the risk of recurrence. It is most important to determine and address the cause of bleeding while considering the patient's individual risk-benefit profile with regards to risk of thrombosis with DOAC discontinuation versus risk to patient with ongoing bleeding. Specialist consultation is recommended if the risk of thrombosis is uncertain or if specialty involvement is required to mitigate bleeding (e.g., *RACE consult line*).

Overall, DOACs do not usually require reversal because of their short half-life.[38] However, emergency reversal may be indicated for life-threatening bleeding situations or when urgent interventions are required.[38] Dabigatran is currently the only DOAC with a dedicated reversal agent. Refer to *BC Guidelines Oral Anticoagulants: Elective Interruption and Emergency Reversal*, *Canadian Cardiology Society NVAF* guidelines, and *Thrombosis Canada* for more information on bleeding management. In general:

- For most **minor bleeding** events (e.g., minor lesions, simple tooth extraction) DOACs can be continued with the application of local measures. Prolonged pressure may be required.
- For **moderate bleeding** that is challenging to control, consider brief DOAC interruption (e.g.,1-2 days). Because DOACs have a short duration of action, prolonged interruption increases the risk of thrombosis substantially.
- For **potentially life-threatening bleeding** (e.g., severe GI bleeding, intracranial bleeding) or bleeding into a critical site (e.g., joint), the DOAC should be stopped immediately, and the patient should seek care at the closest emergency department.

Resources

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Abbreviations:

aPTT	Activated partial thromboplastin clotting time
CBC	Complete blood count
CrCl	Creatinine clearance
DOAC	Direct oral anticoagulant
eGFR	estimated glomerular filtration rate
HIV	Human immunodeficiency virus
LMWH	Low molecular weight heparin
NVAF	Non-valvular atrial fibrillation
VTE	Venous thromboembolism

Resources

Clinical Decision Support Tools

- *Child-Pugh Calculator*
- *Cockcroft-Gault Calculator*
- *PharmaCare Special Authority*: Provides benefit status for medication coverage and specific medical circumstances of coverage, depending on BC PharmaCare plan rules.
- *Thrombosis Canada periprocedural algorithm tool*

Consultation Supports

- *RACE: Rapid Access to Consultative Expertise Program*: RACE means timely telephone advice from specialist for Physicians, Medical Residents, Nurse Practitioners, Midwives, all in one phone call.
  - Monday to Friday 0800 – 1700
  - Online at *www.raceapp.ca* or though *Apple* or *Android* mobile device.
  - Local Calls: 604–696–2131 | Toll Free: 1–877–696–2131
  - For a complete list of current specialty services visit the *Specialty Areas page*.
- *PathwaysBC*: An online resource for current and accurate referral information for specialists and specialty clinics, including wait times and areas of expertise.

Related Guidelines

- *Thrombosis Canada*
- *HealthLink BC*
- *BC Guidelines: Warfarin*
- *BC Guidelines: Oral Anticoagulants: Elective Interruption & Emergency Reversal*
- *BC Guidelines: Stroke and Transient Ischemic Attack*
- *BC Guidelines: Atrial Fibrillation*
- *BC Guidelines: Venous Thromboembolism*

Additional Resources

- *Health Data Coalition*: An online, physician-led data sharing platform that can assist you in assessing your own practice in areas such as chronic disease management or medication prescribing.
- *General Practice Services Committee*:
  - Practice Support Program: Offers focused, accredited training sessions for BC physicians to help improve practice efficiency and support enhanced care.
  - Chronic Disease Management and Complex Care Incentives: Compensates for the time and skill needed to work with patients with complex conditions or specific chronic diseases.
- *QuitNow Smoking Cessation Program*: Provides one-on-one coaching support and valuable resources in multiple languages. Phone: 1-877-455-2233 or Email: *quitnow@bc.lung.ca*
- *Smokers' Helpline*: 1-866-366-3667
- *Public Health Agency of Canada*: Provides resources to help patients make wise choices about healthy living, including increasing physical activity and eating well.
- *US Centre for Disease Control*
- *British Columbia Centre of Disease Control (BCCDC)*

Appendices

- *Appendix A: DOAC Drug Interactions*
- *Appendix B: Switching Between Anticoagulant Therapies*

Associated Documents

- BC Pharmacare: *Special Authority Request Form 5391 – Apixaban /Dabigatran/ Rivaroxaban for Atrial Fibrillation*

This guideline is based on scientific evidence current as of the effective date.

This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association, and adopted by the Medical Services Commission.

For more information about how BC Guidelines are developed, refer to the GPAC Handbook available at *BCGuidelines.ca: GPAC Handbook*.

THE GUIDELINES AND PROTOCOLS ADVISORY COMMITTEE

The principles of the Guidelines and Protocols Advisory Committee are to:

- encourage appropriate responses to common medical situations
- recommend actions that are sufficient and efficient, neither excessive nor deficient
- permit exceptions when justified by clinical circumstances

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Disclaimer

Appendix A: DOAC Drug Interactions

This table is not an exhaustive list of all contraindicated and potential drug-drug interactions. Please consult product monographs, *drug interaction checkers* (e.g., Lexicomp), and/or a pharmacists, as needed.

<table>
<tr><th></th><th>Dabigatran</th><th>Apixaban and Rivaroxaban</th><th>Edoxaban</th></tr>
<tr><td>CONTRAINDICATED</td><td>↑ Bleed Risk (Strong inhibitors of P-gp)1
• ketoconazole
• glecaprevir/pibrentasvir (Maviret)</td><td>↑ Bleed Risk (Strong inhibitors of CYP3A4 and P-gp)[2,3]
• azole-antimycotics (e.g., itraconazole[2])
• HIV protease inhibitors (e.g., ritonavir)
• cobicistat[3]</td><td>No contraindicated drug interactions aside from drugs generally contraindicated with DOACs, e.g., anticoagulants.</td></tr>
<tr><td rowspan="2">AVOID USE</td><td colspan="2">↑ Bleed Risk (Inhibitors of P-gp)[1,3]
• dronedarone</td><td>↑ Bleed Risk (Inhibitors of P-gp)[4] see below for dose reductions[4]</td></tr>
<tr><td colspan="3">↑ Thromboembolic Risk (Strong inducers of CYP3A4 and/or P-gp)[1,2,3,4,5]
• carbamazepine
• phenobarbital
• phenytoin
• rifampin
• St. John's Wort</td></tr>
<tr><td rowspan="2">USE WITH CAUTION</td><td>↑ Bleed Risk (Inhibitors of P-gp):[1]
• amiodarone
• cyclosporine, tacrolimus
• itraconazole, posaconazole
• HIV protease inhibitors (e.g., ritonavir)
• SSRIs/SNRIs

Where concomitant use cannot be avoided, administer dabigatran ≥ 2 hrs prior to use of:
• antacids (e.g., sodium bicarbonate)
• quinidine
• verapamil</td><td>↑ Bleed Risk (Inhibitors of P-gp and/or CYP3A4):[2,3]
• cyclosporine
• clarithromycin
• diltiazem
• SSRIs/SNRIs</td><td>↑ Bleed Risk (Inhibitors/substrates of P-gp):[4]
Concomitant use of the following drugs requires dose reduction to edoxaban 30 mg once daily:
• cyclosporine
• dronedarone
• erythromycin
• ketoconazole
• quinidine</td></tr>
<tr><td colspan="3">↑ Bleed Risk (Other)
• Platelet inhibitors, e.g., clopidogrel
• Non steroidal anti-inflammatory drugs (NSAIDs), e.g., ibuprofen
• Supplements known to increase bleed risk, e.g., garlic[6]</td></tr>
</table>

Abbreviations: CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4 isoenzymes; P-gp = P-glycoprotein; SSRI/SNRI = Selective serotonin reuptake inhibitors / serotonin and norepinephrine reuptake inhibitors; ↑ = increase; ↓ = decrease.

References:

1. Boehringer Ingelheim Canada Ltd. Product monograph Pradaxa (dabigatran etexilate) capsules [Internet]. 2020 [cited 2022 Feb 28].
2. Pfizer Canada Inc. Product monograph Eliquis (apixaban) tablets [Internet]. 2019 [cited 2022 Feb 28].
3. Bayer Inc. Product monograph Xarelto (rivaroxaban) tablet [Internet]. 2021 [cited 2022 Feb 28].
4. Servier Canada Inc. Product monograph Lixiana (edoxaban) tablet [Internet]. 2021 [cited 2022 Feb 28].
5. Lexicomp Drug Interactions. 2022. [cited 2022 October 3].
6. NOAC/DOACS: Comparisons and Frequently asked questions. Thrombosis Canada [Internet]. 2021 [cited 2022 October 3].

Appendix B: Switching Between Warfarin and DOAC

Changes in anticoagulant therapy are associated with a transient increased risk of stroke and systemic embolism. However, switching may be indicated for patients who are frequently outside the therapeutic INR range or those who cannot adhere to regular laboratory monitoring.[28] *Figure 1: Switching from Warfarin to a DOAC* and *Figure 2: Switching from a DOAC to Warfarin* provides a reasonable approach to switching between anticoagulant therapies.

Figure 1: Switching from Warfarin to a DOAC

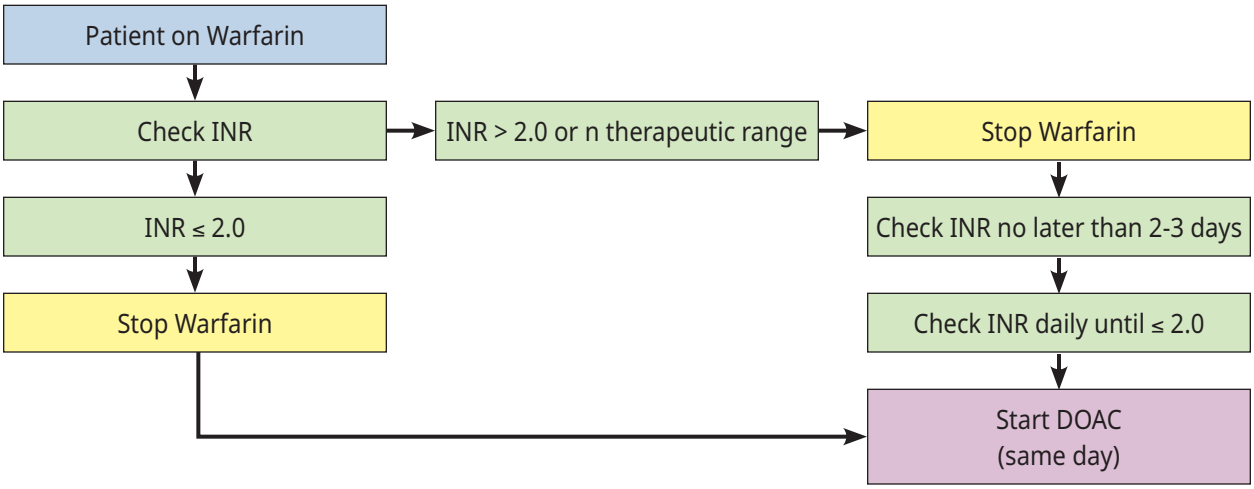

Figure 2: Switching from a DOAC to Warfarin