DOACs: Comparison And Frequently-asked Questions

Thrombosis Canada
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Objectives:

- To summarize characteristics of the direct oral anticoagulants (DOACs) currently available in Canada.
- To address common practical issues related to DOAC use.
- To address frequently asked questions regarding DOACs.

Background:

The DOACs, which consist of apixaban, dabigatran, edoxaban, and rivaroxaban are used for the prevention and treatment of venous thromboembolism (VTE) and for stroke prevention in atrial fibrillation (AF). Practical advantages of DOACs over warfarin include fixed once- or twice-daily oral dosing without the need for coagulation test monitoring, fewer drug interactions and no known dietary interactions. Like warfarin, DOACs increase the risk for bleeding and should be administered under close clinical monitoring. Practical issues regarding the everyday use of DOACs will be addressed in this guide.

Practical and Lifestyle Issues:

Can DOACs be taken with meals? Rivaroxaban 15 mg and 20 mg tablets should be taken with meals to enhance absorption. Rivaroxaban, edoxaban and apixaban can be crushed and taken with soft foods such as applesauce. Apixaban, dabigatran, edoxaban can be taken with or without meals. Taking dabigatran with meals may reduce dyspepsia. Dabigatran capsules should not be opened, broken, or chewed before swallowing.

Are there any foods or beverages that need to be avoided with DOACs?Unlike with warfarin, there are no known dietary interactions with DOACs. In addition, there is no evidence that drinking grapefruit juice affects the effectiveness or safety of DOACs. In general, it is acceptable for patients taking a DOAC to drink alcoholic beverages in moderation (e.g. a glass of wine with a meal).

What if stomach upset occurs after starting a DOAC? Stomach upset occurs in up to 10% of patients who start dabigatran (contains tartaric acid pellets to aid absorption), but is uncommon with apixaban, edoxaban, or rivaroxaban. Taking dabigatran with meals can reduce the risk of stomach upset and the problem often improves on its own after a few days. Caution is advised regarding the use of antacids as the absorption of dabigatran is decreased when co-administered with antacids containing aluminum, magnesium, or calcium.

Can DOACs be placed in a dosette? Apixaban, edoxaban, and rivaroxaban can be placed in a dosette. Dabigatran needs to be kept in the medication packaging until it is taken, as there is potential for product breakdown if the capsule is exposed to moisture; it can be placed in a dosette as long as it remains sealed in its unopened blister pack.

What if a DOAC dose is missed? If a dose is missed, the next dose should *not* be doubled. Instead, it is advised to continue at the usual dose starting with the next scheduled dose. The exception is if patients are taking rivaroxaban, 15 mg twice daily, during the first 3 weeks after VTE. In this case, if a morning dose is missed, the morning dose should be taken as soon as possible so that 2 of the 15 mg tablets are taken that day. This also applies if patients are taking apixaban, 10 mg twice daily, during the first week after VTE. In this case, if a morning dose is missed, the morning dose should be taken as soon as possible so that two doses of 10 mg are taken that day.

What if the patient needs dental work? For patients who need minor dental work such as teeth cleaning or an uncomplicated tooth extraction, it is probably safe to continue the DOACs around the time of the procedure; consideration can also be given to the use of tranexamic acid mouthwash (a pro-hemostatic, antifibrinolytic agent) before and after the procedure. For the management of patients who require other procedures or surgery, see the **Clinical Guide: DOACs: Peri-Operative Management.**

What if the patient has a prosthetic heart valve? In patients with a mechanical heart valve, DOACs are contraindicated. In patients with a bioprosthetic (tissue) heart valve, DOACs may be used as indicated for treatment of VTE or AF once the high risk period post-implantation has passed.

Can DOACs be crushed or given through an enteral feeding tube?

Dabigatran: The capsule must be taken orally and cannot be placed down an enteral feeding tube. The capsule contents cannot be opened, crushed, or altered in any way.

Rivaroxaban: Rivaroxaban can be cut, crushed, or mixed in solution. Rivaroxaban may also be given to patients via feeding tube if the tube is placed within the stomach.

Apixaban: Apixaban can be cut or crushed. If apixaban is administered via NG access, use of a crushed tablet suspended in D5W is preferable to mixing or flushing with nutritional supplement.

Edoxaban: Edoxaban can be cut or crushed.

DOACs and Other Medications:

Can an NSAID be taken with DOACs? In general, long-term use of a non-steroidal anti-inflammatory drug (NSAID) combined with a DOAC should be avoided. Acetaminophen is preferred over an NSAID for joint pain, headache, or cold or flu-like symptoms. If there is a need for longer periods of treatment with an NSAID, further discussion between the patient and doctor is warranted.

Can an antacid be taken with DOACs? Absorption of dabigatran in the gastrointestinal (GI) tract requires an acid milieu. However, although the use of PPIs and H_2-blockers leads to slightly reduced bioavailability of the drug, it has no effect on clinical efficacy. Therefore, intake of these medications is not a concern with dabigatran (or with the other DOACs). Caution is advised regarding the use of over-the-counter antacids as the absorption of dabigatran is decreased when co-administered with antacids containing aluminum, magnesium, or calcium.

Are there other medications that should be avoided when taking a DOAC? There are certain medications that should be avoided when taking a DOAC. These are listed in **Table 1**. If one of these drugs is medically indicated over an extended duration, an alternative anticoagulant to a DOAC should be considered. Consultation with an appropriate speciality (e.g. cardiology, hematology, neurology, infectious disease) is advisable in such situations.

Can herbal medications be taken with a DOAC? Patients should avoid taking St. John's Wort if they are taking a DOAC, as this drug may reduce DOAC levels. There are no other known restrictions for other herbal medications; although, in general, those associated with an increased risk of bleeding, such as garlic or curcurmin (turmuric) supplements, should generally be avoided.

Table 1: Comparison of Key Properties of NOACs

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)
Clinical Indications and Doses				
Atrial fibrillation (indefinite duration)	150 mg or 110 mg twice daily	20 mg or 15 mg daily	5 mg or 2.5 mg twice daily	60 mg or 30 mg daily
Acute VTE (3 to 6 months)	150 mg twice daily (after 5-10 day course of LMWH)*	20 mg daily (15 mg twice daily for initial 21 days)	5 mg twice daily (10 mg twice daily for initial 7 days)	60 mg or 30mg daily (after 5-10 day course of LMWH)*
Secondary prevention of VTE	150 mg twice daily	20 mg daily or 10 mg daily	5 mg or 2.5 mg twice daily	60 mg or 30 mg daily
VTE prevention after knee or hip replacement surgery (14 to 30 days)	110 mg (initial dose) then 220 mg daily	10 mg daily	2.5 mg twice daily	Not applicable
Stable CAD or PAD	Not applicable	2.5mg twice daily with daily low dose ASA	Not applicable	Not applicable
Key Pharmacologic Properties				
Mechanism of action	Direct factor IIa (thrombin) inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Renal clearance	80%	33%	25%	50%
Half-life				
Normal to mild impairment (CrCl ≥50 mL/min)	7-17 hours	7-11 hours	8-12 hours	10-14 hours
Moderate renal impairment (CrCl 30-49 mL/min)	17-20 hours	7-11hours	8-12 hours	
Severe renal impairment (CrCl <30 mL/min)	21-35 hours	11-15 hours	12-17 hours	
Onset of action (after oral intake)	1-3 hours	1-3 hours	1-3 hours	1-3 hours
Key Practical Properties				
Food or alcohol interactions	none	*needs to be taken with food*	none	none
Drug Interactions				
Substrate of P-gp	Yes	Yes	Yes	Yes
Substrate of CYP3A4	No	Yes (~18%)	Yes (~25%)	Minor (<10%)
Examples of medications that INCREASE levels	amiodarone, dronedarone, cyclosporine, quinidine, azole antifungals (e.g. ketoconazole, itraconazole, posaconazole), and HIV protease inhibitors (e.g. ritonavir)	azole antifungals (e.g. ketoconazole, itraconozole, voriconazole, and posaconazole), HIV protease inhibitors (e.g. ritonavir),and macrolide antibiotics (e.g. clarithromycin)	azole antifungals (e.g. ketoconazole, itraconozazole, voriconazole, posaconazole), HIV protease inhibitors (e.g. ritonavir), macrolide antibiotics (e.g. clarithromycin)	cyclosporine, dronedarone, quinidine, azole antifungals (e.g. ketoconazole, itraconozaole), HIV protease inhibitors (e.g. ritonavir), macrolide antibiotics (e.g. clarithromycin
Examples of medications that DECREASE levels	anticonvulsants (e.g. phenytoin, carbamazepine), rifampin and St. John's Wort	anticonvulsants (e.g. phenytoin, carbamazepine), rifampin and St. John's Wort	anticonvulsants (e.g. phenytoin, carbamazepine), rifampin and St. John's Wort	anticonvulsants (e.g. phenytoin, carbamazepine), rifampin and St. John's Wort
Antidote	Idarucizumab	Andexanet alfa †	Andexanet alfa†	Andexanet alfa (not approved by Health Canada for edoxaban reversal)†

*dabigatran and edoxaban require an initial 5-10 day course of LMWH before they are started (see the **Clinical Guides:** **Deep Vein Thrombosis (DVT): Treatment** **and** **Pulmonary Embolism (PE): Treatment**).
†In the case of life-threatening bleeding Prothrombin Complex Concentrates (Octaplex, Beriplex) are used as pro-hemostatic agents and may be effective in decreasing critical bleeding in patients on Anti-Xa inhibitors.

Monitoring and Follow-Up of Patients Taking a DOAC:

Do patients taking a DOAC need routine clinical follow-up and blood testing? Yes. It is prudent to perform routine follow-up at least every 6-12 months in patients who are receiving long-term treatment with a DOAC. This is required to confirm the patient has an ongoing indication for DOAC, check for bleeding complications, assess the relative risks of thromboembolism and bleeding complications, perform a complete count (CBC) and assessment of kidney function (creatinine), and review medication interactions (prescription, over the counter, herbal supplements). These factors may warrant adjustment of the DOAC dose, change from one DOAC to another DOAC, or change from a DOAC to warfarin. In addition, periodic follow-up is useful to check for adherence to DOAC treatment, and to plan for treatment interruptions for upcoming procedures. Thrombosis Canada has developed a tool for yearly **DOAC follow-up.**

Do patients taking a DOAC need routine coagulation testing? No. Tests of coagulation such as the INR or aPTT do not need to be done routinely in patients who are receiving a DOAC. However, DOACs can variably affect these blood tests; cautious and informed interpretation is needed if these tests are done for other reasons (e.g. before surgery). A summary of the effect of DOACs on coagulation tests is shown in **Table 2**. (See also the **Clinical Guides:** **DOACs: Coagulation Tests** and **DOACs: Peri-Operative Management**).

How does one switch from warfarin to a DOAC? After stopping warfarin, the patient should wait until the INR is less than 2.0 before starting dabigatran or apixaban and less than or equal to 2.5 for rivaroxaban and edoxaban. This is because the onset of action of the DOAC is rapid (peak effect 1-3 hours after ingestion), while the offset of action of warfarin is slower. If INR testing is not readily available, it is reasonable to wait 2-3 days after the last dose of warfarin before starting a DOAC. Note, if the INR is supratherapeutic, it will take longer to achieve an INR of 2.0 or lower.

Table 2: Summary of Testing for Measurement of DOAC Anticoagulant Effect†

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)
aPTT	Nonlinear prolongation with increasing dose, a normal result does not exclude an important drug effect	Minimal effect	Minimal effect	Variable effect; a normal result does not exclude an important drug effect
Thrombin clotting time (TCT) Dilute TCT	Normal result excludes an important drug effect dilute TCT (Hemoclot assay) most reliable/accurate	No effect	No effect	No effect
PT/INR	Variable effect	Variable effect; INR frequently 1.4-1.6; a normal result does not exclude an important drug effect	Minimal effect	Variable effect; a normal result does not exclude an important drug effect
anti-factor Xa assay	No effect	Most reliable/accurate	Most reliable/accurate	Most reliable/accurate

†Laboratory tests may not reliably reflect levels of anticoagulation with DOACs and the routinely available tests should not be used for this purpose (**See the Clinical Guide: DOACs: Coagulation Tests**).

Acute Medical Emergencies in Patients Receiving a DOAC:

What if my patient has an acute ischemic stroke? In patients who have an acute stroke and are receiving a DOAC, the management should be similar to other patients with an ischemic stroke. In general, compliance with the DOAC should be assessed. Where appropriate, thrombolytic therapy should be considered, especially if sufficient time has elapsed since the last DOAC dose such that there would be little residual anticoagulant effect. Note that a normal aPTT and/or INR/PT cannot be used as reassurance that intravenous thrombolysis can be safely given to patients with acute ischemic stroke. There is currently no consensus about when intravenous thrombolysis can be safely administered in patients on DOACs. In the emergent setting of stroke thrombolysis, the best tool to determine when the last DOAC dose was taken remains the clinical history. Consultation with a neurologist is strongly advised in these situations. Use of thrombin clotting test or calibrated anti-Xa assay to determine the presence of residual circulating DOAC, if available with sufficient turnaround time, can be helpful when ambiguity remains about last DOAC intake. (See the **Clinical Guide: Stroke Thrombolysis and Endovascular Therapy**).

What if my patient has an acute coronary syndrome? In patients who are receiving a DOAC and suffer an acute coronary syndrome, the management should be similar to other patients with such an event. Consultation with a cardiologist is strongly advised in these situations. (See also the **Clinical Guide: Anticoagulation in Patients Requiring Antiplatelet Therapy**).

What if my patient has major trauma or a serious bleed? In such patients, emphasis should be on supportive care and treating the underlying cause of bleeding (See the **Clinical Guide: DOACs: Management of Bleeding**). In selected circumstances for patients on dabigatran, administration of the antidote idarucizumab may be considered. For patients on Factor-Xa inhibitors, administration of prothrombin

complex concentrates (Octaplex, Beriplex) may be considered. Consultation with a hematologist or thrombosis specialist is advised in these situations.

Comparison of DOACs:

Are there any studies comparing the DOACs? There are no "head-to-head" randomized trials comparing different DOACs. All studies done to date have compared one DOAC with warfarin for stroke prevention in AF and for the treatment of VTE, or with LMWH for VTE prophylaxis and for the treatment of cancer-associated thrombosis. Large observational studies have suggested lower rates of major bleeding with apixaban than with rivaroxaban, but this has not been confirmed in prospective or randomized trials to date.

Which DOAC is the most effective and which is the safest in patients with AF? This is currently impossible to answer because the randomized trials comparing each DOAC to warfarin (INR 2.0-3.0) for stroke prevention in AF differed in terms of trial design, patient population studied, and medication dose regimens used. Each DOAC has potential advantages and drawbacks. Choosing which of these drugs is best for your patient should include an assessment of 1) your patient's risk profile for stroke; 2) your patient's risk profile for bleeding; and 3) the presence of comorbid conditions (e.g. prior stroke, renal dysfunction).

Which DOAC is the most effective and which is the safest in patients with acute VTE? As with AF, there are currently no "head-to-head" trials comparing the DOACs for the treatment of acute VTE.

How should DOACs be used in patients with impaired renal function? The DOACs differ in terms of how they should be used in patients who have impaired renal function. **Table 3** provides a suggested guide for using DOACs in patients with AF and impaired renal function. For patients with VTE on edoxaban, the dose should be reduced to 30 mg daily if there is moderate renal impairment (CrCl 30-50 mL/min). Note there is no dose reduction for renal impairment for the acute treatment of VTE with the other DOACs (dabigatran, apixaban, rivaroxaban).

Table 3: Suggested use of DOACs according to patient renal function for stroke prevention in AF[‡]

DOAC	CrCl (mL/min)	Drug dose	Comment
Dabigatran	≥ 50	150 mg twice daily	110 mg dose in patients ≥ 80 years and consider of >75 years of age and at increased risk for bleeding Measure CrCl every 12 months
	30-49	150 mg twice daily	110 mg dose in patients ≥ 80 years and consider of >75 years of age and at increased risk for bleeding Measure CrCl every 6 months *and* with acute illness Consider avoiding if deteriorating renal function
	< 30	Avoid dabigatran	Consider warfarin as alternative anticoagulant
Rivaroxaban	≥ 50	20 mg daily	Measure CrCl every 12 months *and* with acute illness
	30-49	15 mg daily	Measure CrCl every 6 months *and* with acute illness
	15 - 30	15 mg daily	Use with caution. Measure CrCl every 3 months *and* with acute illness
	<15	Avoid rivaroxaban	Consider warfarin as an alternative anticoagulant
Apixaban	≥ 50	5 mg twice daily	Measure CrCl every 12 months *and* with acute illness 2.5 mg twice daily in patients with 2 or more of the following: **A**ge ≥ 80 years; **B**ody weight ≤ 60 kg; **C**reatinine ≥ 133 µmol/L
	30-49	5 mg twice daily	Measure CrCl every 6 months *and* with acute illness 2.5 mg twice daily in patients with 2 or more of the following: **A**ge ≥ 80 years; **B**ody weight ≤ 60 kg; **C**reatinine ≥ 133 µmol/L
	15-30	No dose recommendations can be made	Very limited clinical data
	< 15	Avoid apixaban	Consider warfarin as alternative anticoagulant*
Edoxaban	≥50	60 mg daily	Reduce dose to 30 mg daily if weight <60 kg or if concomitant use of P-gp inhibitor (except amiodarone and verapamil). Measure CrCl every 12 months
	15-50	30 mg daily	Measure CrCl every 6 months *and* with acute illness Consider avoiding if deteriorating renal function
	<15	Avoid edoxaban	Consider warfarin as an alternative anticoagulant

‡It is advised to consult with a specialist if there is uncertainty about the appropriate NOAC drug and dose regimen and if warfarin provides a better oral anticoagulation option for individual patients.

Other Relevant Thrombosis Canada Clinical Guides:

- Anticoagulation in Patients Requiring Antiplatelet Therapy
- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis (DVT): Treatment
- DOACs: Coagulation Tests
- DOACs: Management of Bleeding
- DOACs): Peri-Operative Management
- Edoxaban (Lixiana®)
- Pulmonary Embolism (PE): Diagnosis
- Pulmonary Embolism (PE): Treatment
- Rivaroxaban (Xarelto®)
- Stroke Prevention in Atrial Fibrillation
- Stroke Thrombolysis and Endovascular Therapy
- Thromboprophylaxis: Orthopedic Surgery

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