NOACS/DOACS*: COMPARISON AND FREQUENTLY-ASKED QUESTIONS

Thrombosis Canada
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OBJECTIVES:

- To provide a comparison of the newer direct oral anticoagulants (DOACs) currently available in Canada.
- To address frequently-asked questions regarding DOACs.

BACKGROUND:

The newer DOACs, which consist of dabigatran, rivaroxaban, apixaban, and edoxaban, are used for the prevention and treatment of VTE and for stroke prevention in AF. Practical advantages of DOACs over warfarin include fixed, once- or twice-daily, oral dosing without the need for coagulation test monitoring, relatively fewer known drug interactions, and no known food 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? Dabigatran capsules should be taken with meals but the capsules should not be opened, broken or chewed before swallowing. Rivaroxaban should be taken with meals to enhance absorption; the pill can be crushed and taken with soft foods such as applesauce. Apixaban and edoxaban can be taken with or without meals.

Are there any foods or beverages that need to be avoided with DOACs? Unlike with warfarin, there are no known food interactions with DOACs, so there are no food restrictions when taking these medications. 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 alcohol beverages in moderation (e.g., glass of wine with a meal) as it is for patients on warfarin.

What if stomach upset occurs after starting a DOAC? Stomach upset occurs in up to 10% of patients who start dabigatran but is less common with rivaroxaban, apixaban or edoxaban. Taking dabigatran with meals can reduce the risk of stomach upset and the problem often improves on its own after a few days. Antacids may help but relevant studies are lacking.

Can DOACs be placed in a dosette? Rivaroxaban, apixaban and edoxaban can be placed in a weekly or monthly 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 2 of the 10 mg tablets are taken that day.

What if the patient needs dental work? For patients who need minor dental work such as teeth cleaning or a tooth extraction, it is probably safe to continue the DOACs around the time of the procedure; consideration can also be given to the using 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: NOACs/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, but this has not been formally studied.

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. It is probably safe to combine the use of low dose NSAIDs with a DOAC for short, 3-5 day periods, for example, to treat acute joint pain. 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 or acetaminophen, further discussion between the patient and doctor is warranted.

Can an antacid be taken with DOACs? Absorption of dabigatran in the GI tract requires an acid milieu. However, though use of PPIs and H_2-blockers leads to slightly reduced bioavailability of the drug, it has no effect on clinical efficacy. Therefore, antacid intake is not a concern with dabigatran (or with the other DOACs).

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. There are no other known restrictions for other herbal medications.

TABLE 1: COMPARISON OF KEY PROPERTIES OF DOACS

	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	20 mg daily (15 mg twice daily for initial 21 days)	5 mg twice daily (10 mg twice daily for initial 7 days)	30 or 60 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
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% (active drug)	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	• amiodarone, quinidine, azole antifungals (e.g. ketoconazole), ritonavir increase dabigatran levels • rifampin reduces dabigatran levels	• azole antifungals (e.g. ketoconazole), ritanovir, clarithromycin increase rivaroxaban levels • anticonvulsants (e.g. phenytoin, carbamazepine), rifampin reduce rivaroxaban levels	• azole antifungals (e.g. ketoconazole), ritanovir, clarithromycin likely increase apixaban levels • anticonvulsants (e.g. phenytoin, carbamazepine), rifampin likely reduce apixaban levels	• azole antifungals (e.g. ketoconazole), ritanovir, clarithromycin likely increase edoxaban levels • anticonvulsants (e.g. phenytoin, carbamazepine), rifampin likely reduce edoxaban levels
Antidote	Idarucizumab	Andexanet alfa (not yet approved by Health Canada)	Andexanet alfa (not yet approved by Health Canada)	Andexanet alfa (not yet approved by Health Canada)

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)
Laboratory Measurement of Anticoagulant Effect‡	• aPTT or thrombin clotting time (TCT) • dilute TCT (Hemoclot assay)	• prothrombin time (PT)/INR anti-factor Xa assay	• PT/INR (has minimal effect) • anti-factor Xa assay	• anti-factor Xa assay

‡laboratory tests may not reliably reflect levels of anticoagulation with DOACs (See the Clinical Guide: NOACs/DOACs: Coagulation Tests).

Monitoring and follow-up of patients taking a DOAC:

Do patients taking a DOAC need routine clinical follow-up? 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 check for bleeding complications, to assess the relative risk of thromboembolism and bleeding complications, and to assess kidney function. 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 patient compliance with their DOAC treatment, to assess concomitant medications, and to plan for treatment interruptions for upcoming procedures.

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). (See also the Clinical Guides: NOACs/DOACs: Coagulation Tests and NOACs/DOACs: Peri-Operative Management).

Do patients taking a DOAC need any routine blood testing? Yes. It is prudent for patients who are receiving a DOAC to have an assessment of kidney function every 6-12 months, since worsening of renal function may warrant change in the dose of a DOAC, switching from one DOAC to another, or switching from a DOAC to warfarin.

How does one switch from warfarin to a DOAC? After stopping warfarin, the patient should wait until the INR is 2.0 or lower before starting a DOAC. 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.

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 (i.e. 12-18 hours) so there is little residual anticoagulant effect. The addition of an antiplatelet drug should also be considered. Note that the aPTT, INR and PT cannot reassure that intravenous thrombolysis can be safely given to patients with acute ischemic stroke. There is also 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.

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 Guides: Non-ST Elevation Acute Coronary Syndrome: Outpatient Antithrombotic Management and ST Elevation Myocardial Infarction: Outpatient Antithrombotic Management).

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: NOACs/DOACs: Management of Bleeding). 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 the DOACs (apixaban, dabigatran, rivaroxaban). All of the studies done to-date have compared one DOAC with conventional anticoagulant therapy, typically warfarin, for stroke prevention in AF and for the treatment of VTE.

Which DOAC is the most effective and which is the safest in patients with AF? This is currently impossible to answer because the 3 randomized trials comparing apixaban (ARISTOTLE), dabigatran (RE-LY) or rivaroxaban (ROCKET-AF) 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). **Table 2** suggests situations where some DOACs may be preferable.

TABLE 2: SUGGESTED USE OF DOACS ACCORDING TO PATIENT CHARACTERISTICS FOR STROKE PREVENTION IN AF†

PATIENT CHARACTERISTIC	SUGGESTED DOAC REGIMEN	COMMENT
Patients with AF at high risk for stroke (e.g. $CHADS_2 \geq 3$) or with prior stroke	dabigatran 150 mg twice daily	This dose of dabigatran conferred the greatest risk reduction in stroke compared with warfarin
	rivaroxaban 20 mg daily	More patients with prior stroke were studied with rivaroxaban
	apixaban 5 mg twice daily	The greatest benefit to prevent stroke compared with warfarin occurred in patients with $CHADS_2 \geq 3$
Patients with AF at high risk for bleeding	apixaban 5 mg twice daily	This dose of apixaban conferred a decrease in the risk of major bleeding compared with warfarin
	dabigatran 110 mg twice daily	This dose of dabigatran conferred a decrease in the risk of major bleeding compared with warfarin
	edoxaban, 60 mg daily	This dose of edoxaban conferred a decrease in the risk of major bleeding compared with warfarin
Elderly (≥ 80 years) patients with impaired renal function (e.g. CrCl < 50 mL/min)	apixaban 2.5 mg twice daily	Apixaban was associated with a reduced risk of bleeding in patients with impaired renal function
	rivaroxaban 15 mg once daily	A reduced rivaroxaban dose was studied in patients with impaired renal function
	edoxaban, 30 mg daily	A reduced edoxaban dose was studied in patients with impaired renal function

†Alternative options may also be reasonable. It is advised to consult with a specialist if there is uncertainty about the appropriate DOAC drug and dose regimen for individual patients; AF, atrial fibrillation.

Which DOAC is the most effective and which is the safest in patients with acute VTE? As with AF, there are 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 impaired renal function.

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	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding or in the elderly (e.g. age ≥ 80 years) Measure CrCl every 12 months
	30-49	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding (e.g. age ≥ 80 years) 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
	30-49	15 mg daily	Measure CrCl every 6 months *and* with acute illness Consider avoiding if deteriorating renal function
	< 30	Avoid rivaroxaban	Consider warfarin as alternative anticoagulant
Apixaban	≥ 50	5 mg twice daily	2.5 mg twice daily in patients with 2 of following: (1) creatinine ≥ 133 µmol/L; (2) age ≥ 80 years; (3) body weight ≤ 60 kg Measure CrCl every 12 months
	25-49	5 mg twice daily	2.5 mg twice daily in patients with 2 of following: (1) creatinine ≥ 133 µmol/L; (2) age ≥ 80 years; (3) body weight ≤ 60 kg Measure CrCl every 6 months *and* with acute illness
	15-24	No dose recommendations can be made	Very limited clinical data with apixaban Consider warfarin as alternative anticoagulant
	< 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.
	30-50	30 mg daily	Measure CrCl every 6 months *and* with acute illness Consider avoiding if deteriorating renal function
	<30	Avoid edoxaban	Consider warfarin as an alternative anticoagulant

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

OTHER RELEVANT GUIDES:

- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis (DVT): Treatment
- NOACs/DOACs: Coagulation Tests
- NOACs/DOACs: Management of Bleeding

- NOACs/DOACs): Peri-Operative Management
- Edoxaban (Lixiana®)
- Non-ST Elevation Acute Coronary Syndrome: Outpatient Antithrombotic Management
- Pulmonary Embolism (PE): Diagnosis
- Pulmonary Embolism (PE): Treatment
- Rivaroxaban (Xarelto®)
- ST Elevation Myocardial Infarction: Outpatient Antithrombotic Management
- Stroke Prevention in Atrial Fibrillation
- Thromboprophylaxis: Orthopedic Surgery

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

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