

**COMPARISON OF NEW ORAL  
ANTICOAGULANTS AND FREQUENTLY-  
ASKED QUESTIONS FROM PATIENTS  
AND PHYSICIANS**



**Thrombosis** Canada  
**Thrombose** Canada

**TARGET AUDIENCE:** All Canadian health care professionals.

**OBJECTIVES:**

- To provide a comparison of the new oral anticoagulants currently available in Canada.
- To address frequently-asked questions from patients and physicians regarding the new oral anticoagulants.

**ABBREVIATIONS:**

<b>AF</b>	atrial fibrillation
<b>aPTT</b>	activated partial thromboplastin time
<b>CrCl</b>	creatinine clearance
<b>INR</b>	international normalized ratio
<b>NOAC</b>	new oral anticoagulant (dabigatran, rivaroxaban, apixaban)
<b>NSAID</b>	non-steroidal anti-inflammatory drug
<b>NSTEMI</b>	Non-ST elevation myocardial infarction
<b>PT</b>	prothrombin time
<b>STEMI</b>	ST elevation myocardial infarction
<b>TCT</b>	thrombin clotting time
<b>VTE</b>	venous thromboembolism

**FOR PATIENTS: PRACTICAL AND LIFESTYLE ISSUES**

**What if I miss doses of a new oral anticoagulant (NOAC) for 1 or 2 days?** Do not ‘double the dose’ to make up for the missed dose(s). If you have an irregular heartbeat (atrial fibrillation) and 1 or 2 days doses of these drugs are missed, simply continue at the usual dose starting with the next scheduled dose. However, if you are taking rivaroxaban twice daily during the first 3 weeks after a blood clot in the leg or lungs, you should take a missed morning dose as soon as possible and make sure you take 2 of the 15 mg tablets that day.

**Can I place my NOAC medication in a dosette?** Rivaroxaban and apixaban, which come in a pill form, can be placed in a dosette. This is not the case with dabigatran, which is a capsule. Dabigatran needs to be kept in the medication packaging until it is taken, but it can be placed in its blister pack within the dosette.

**Can I take my NOAC medication with meals?** Dabigatran capsules should be taken with food to reduce the risk of stomach upset or can be taken with water. Rivaroxaban should be taken with a meal to enhance absorption; the pill can also be crushed and taken with soft food such as applesauce. Apixaban can be taken with a meal but does not need to be.

**What if I develop heartburn or stomach upset after starting a NOAC?** Many new drugs can cause stomach upset. This problem occurs in up to 10% of patients who start dabigatran and is less common with rivaroxaban or apixaban. Taking the medication with meals can reduce the risk of stomach upset and the problem often improves on its own after a few days. Antacids may help if taken 2 hours after a dabigatran dose. If the problem persists, contact your doctor.

**Are there any foods I need to avoid if I am taking a NOAC?** Unlike with warfarin, there are no known food interactions with NOACs, so there are no food restrictions when taking NOACs.

**Will grapefruit juice affect the way the NOACs work?** There is no evidence that drinking grapefruit juice affects the efficacy or safety of NOACs.

**Can I consume alcoholic beverages if I am taking a NOAC?** In general, it is acceptable to have a glass of wine or beer with a meal when taking a NOAC (or when taking warfarin).

## **FOR PATIENTS: NOACs AND OTHER MEDICATIONS**

**Can I take Tylenol® or drugs such as Advil® if I am taking a NOAC?** In general, long-term use of a NOAC combined with a non-steroidal anti-inflammatory drug (NSAID) such as Advil (ibuprofen) should be avoided. However, it is probably safe to combine a NOAC with an NSAID for short, 3-5 day periods, for example, to treat acute joint pain. Tylenol® (acetaminophen) is preferred over an NSAID for joint pain, headache or if you have cold or flu-like symptoms. If there is a need for longer periods of treatment with an NSAID or acetaminophen, contact your doctor.

**Are there other medications that should be avoided when taking a NOAC?** There are certain medications that should be avoided when taking a NOAC. These are listed in **Table 1**.

**Can I take herbal medications if I am taking a NOAC?** You should avoid taking St. John's Wort (used to treat symptoms of depression) if you are taking a NOAC. There are no restrictions for other herbal medications. It is recommended to check with your doctor if you are uncertain.

## **FOR PHYSICIANS: MONITORING AND FOLLOW-UP OF PATIENTS TAKING A NOAC**

**Do patients taking a NOAC 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 NOAC. This is required to check for bleeding complications, to assess the relative risk for thromboembolism or bleeding complications and to check kidney function. These factors may warrant adjustment of the NOAC dose, change from one NOAC to another NOAC or change from a

NOAC to warfarin. In addition, periodic follow-up is useful to check for patients' compliance with their NOAC treatment, to assess concomitant medications and to plan for treatment interruptions for upcoming procedures.

**Do patients taking a NOAC need routine coagulation testing?** No. Tests of coagulation such as the international normalized ratio (INR) or activated partial thromboplastin time (aPTT) do not need to be done routinely in patients who are receiving a NOAC. However, the NOACs can affect these blood tests, so caution is needed if these tests are done for other reasons (e.g. before surgery) and appropriate interpretation is needed (see [NOACs: Laboratory Monitoring](#) or [NOACs: Perioperative Management](#) guides).

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

**What if I need to switch from warfarin to a NOAC?** After stopping warfarin, you should wait until the INR is 2.0 or lower before starting a NOAC. This is because the onset of action of the NOAC is fast (peak effect 1-3 hours after intake). If INR testing is not readily available, it is reasonable to wait 2-3 days after the last dose of warfarin before starting a NOAC.

**What if my 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 NOACs around the time of the procedure as long as patients receive an oral prohemostatic mouthwash (e.g. tranexamic acid) before and after the procedure, although specific data to support this approach are lacking. Alternatively, the patient can skip one day's dose of the NOAC before the procedure and resume the NOAC on the evening after the procedure. For the management of patients who require other procedures or surgery, see: [NOACs: Peri-Operative Management guide](#)).

**What if my patient has atrial fibrillation and a mechanical heart valve?** In patients with a mechanical aortic or mitral valve, the NOACs are contraindicated.

**What if my patient has atrial fibrillation and a tissue heart valve?** In patients with a bioprosthetic aortic or mitral valve, NOACs can be taken but this is because of the atrial fibrillation indication, not the bioprosthetic heart valve for which only 3 months of warfarin is recommended.

## **FOR PHYSICIANS: ACUTE MEDICAL EMERGENCIES IN PATIENTS RECEIVING A NOAC**

**What if my patient has an acute ischemic stroke?** In patients who are receiving a NOAC and suffer an acute stroke, the management should be the same as with any other patient with an ischemic stroke. Where appropriate, thrombolytic therapy should be considered, especially if sufficient time

has elapsed (i.e. 12-18 hours) since the last NOAC dose so there is little residual anticoagulant effect. Consultation with a neurologist is advised in these situations.

**What if my patient has an acute coronary syndrome?** In patients who are receiving a NOAC and suffer an acute coronary syndrome, the management should be the same as with any other patient with such an event. Consultation with a cardiologist is advised in these situations (see STEMI or NSTEMI guides).

**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 NOACs: Bleeding guide). Consultation with a hematologist or thrombosis specialist is advised in these situations.

## **FOR PATIENTS AND PHYSICIANS: COMPARISON OF NOACS**

**Are there any studies comparing the NOACs?** There are no `head-to-head` randomized trials comparing the NOACs (dabigatran, rivaroxaban, apixaban). All of the studies done to-date have compared a NOAC with conventional anticoagulant therapy, typically warfarin, for stroke prevention in atrial fibrillation and for the prevention or treatment of venous thromboembolism.

**Which NOAC is the most effective and which is the safest in patients with atrial fibrillation?** This is a difficult question to answer because the 3 randomized trials comparing dabigatran (RELY), or rivaroxaban (ROCKET-AF) or apixaban (ARISTOTLE) with warfarin (INR: 2.0-3.0) for stroke prevention in atrial fibrillation differed in terms of trial design, patient population studied, and medication dose regimens used. Each NOAC drug 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 or absence of comorbid conditions (e.g. prior stroke, renal dysfunction). **Table 2** suggests situations where some NOACs may be preferable.

**How should NOACs be used in patients with impaired renal function?** The NOACs differ in terms of how they should be used in patients with impaired renal function. **Table 3** provides a suggested guide for using NOACs in patients with impaired renal function.

## **REFERENCES:**

Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: review and meta-analysis of the literature. *Circulation* 2012;126:2381-2391.

Schulman S, Crowther MA. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. *Blood* 2012;119:3016-3023.

**Table 1: Comparison of Key Properties of NOACs**

	<b>Dabigatran (Pradaxa<sup>®</sup>)</b>	<b>Rivaroxaban (Xarelto<sup>®</sup>)</b>	<b>Apixaban (Eliquis<sup>®</sup>)</b>
<b>Clinical Indications and Doses</b>			
Atrial fibrillation (indefinite duration)	150 mg or 110 mg twice daily	20 mg daily	5 mg twice daily
Acute VTE (3 to 6 months)	150 mg twice daily (not approved)†	20 mg daily (15 mg twice daily for initial 21 days)	5 mg twice daily, 10 mg twice daily for initial 7 days (not approved)†
VTE prevention after knee or hip replacement surgery (14 or 30 days, respectively)	110 mg (initial dose) then 220 mg daily	10 mg daily	2.5 mg twice daily
<b>Key Pharmacologic Properties</b>			
Mechanism of action	Direct factor IIa (thrombin) inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Renal clearance	80%	33% (active drug)	25%
<b>Half-life:</b>			
Normal renal function (CrCl > 80 mL/min)	11 hours	9 hours	9 hours
Mild renal impairment (CrCl 50-80 mL/min)	14 hours	9 hours	9 hours
Moderate renal impairment (CrCl 30-49 mL/min)	15-17 hours	10-15 hours	10-14 hours
Onset of action (after oral intake)	1-3 hours	1-3 hours	1-3 hours
<b>Key Practical Properties</b>			
Food or alcohol interactions	none	none	none
Drug interactions	amiodarone, quinidine, azole antifungals (e.g. ketoconazole), rifampin, ritanovir	azole antifungals (e.g. ketoconazole), ritanovir, rifampin, clarithromycin, anticonvulsants (e.g. phenytoin, carbamazepine)	azole antifungals (e.g. ketoconazole), ritanovir, rifampin, clarithromycin, anticonvulsants (e.g. phenytoin, carbamazepine)
Antidote	none to date	none to date	none to date
<b>Laboratory Measurement of Anticoagulant Effect‡</b>	aPTT or thrombin clotting time (TCT), dilute TCT (Hemoclot assay)	prothrombin time (PT)/INR, anti-factor Xa assay	PT/INR (minimal effect), anti-factor Xa assay

†Not approved for this clinical indication in Canada; ‡laboratory tests may not reliably reflect levels of anticoagulation with NOACs (see: Clinical Guide on NOACs and laboratory testing).

**Table 2: Suggested Use of NOACs According to Patient Characteristics†**

<b>Patient Characteristic</b>	<b>Suggested NOAC Regimen</b>	<b>Comment</b>
Patients with AF at high risk for stroke (e.g. CHADS <sub>2</sub> ≥ 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 <sub>2</sub> ≥ 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
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.

†It is advised to consult with a specialist if there is uncertainty about the appropriate NOAC drug and dose regimen for individual patients; AF, atrial fibrillation.

**Table 3: Suggested Use of NOACs According to Patient Renal Function†**

NOAC	CrCl (mL/min)	Drug Dose	Comment
<b>Dabigatran</b>	> 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
	30-50	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 <i>and</i> with acute illness Consider avoiding if deteriorating renal function
	< 30	Avoid dabigatran	Consider warfarin as alternative anticoagulant
<b>Rivaroxaban</b>	≥ 50	20 mg daily	Measure CrCl every 12 months
	30-49	15 mg daily	Measure CrCl every 6 months <i>and</i> with acute illness Consider avoiding if deteriorating renal function
	< 30	Avoid rivaroxaban	Consider warfarin as alternative anticoagulant
<b>Apixaban</b>	> 50	5 mg twice daily	Measure CrCl every 12 months
	25-50	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 6 months <i>and</i> 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

†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.

*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 information contained herein.*