NEW/NOVEL ORAL ANTICOAGULANTS (NOACs): COMPARISON AND FREQUENTLY-ASKED QUESTIONS

OBJECTIVES:

- To provide a comparison of the new/novel oral anticoagulants (NOACs) currently available in Canada.
- To address frequently-asked questions regarding NOACs.

BACKGROUND:

NOACs, which consist of apixaban, dabigatran and rivaroxaban, are being used increasingly for the prevention and treatment of VTE and for stroke prevention in AF. Practical advantages of NOACs over warfarin include fixed, once- or twice-daily, oral dosing without the need for coagulation test monitoring, few known or defined drug interactions, and no known food interactions. Like warfarin, NOACs increase the risk for bleeding and should be administered with clinical monitoring. Practical issues regarding the everyday use of NOACs will be addressed in this guide.

PRACTICAL AND LIFESTYLE ISSUES:

Can NOACs 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 food such as applesauce. Apixaban can be taken with a meal but does not need to be.

Are there any foods or beverages that need to be avoided with NOACs? Unlike with warfarin, there are no known food interactions with NOACs, so there are no food restrictions when taking NOACs. In addition, there is no evidence that drinking grapefruit juice affects the effectiveness or safety of NOACs. In general, it is acceptable for patients taking a NOAC to drink alcohol beverages in moderation (e.g., glass of wine with a meal) as for patients on warfarin.

What if stomach upset occurs after starting a NOAC? Stomach upset occurs in up to 10% of patients who start dabigatran but 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 but relevant studies are lacking.

Can NOACs be placed in a dosette? Rivaroxaban and apixaban can be placed in a weekly or monthly dosette. Dabigatran needs to be kept in the medication packaging until it is taken; it can be placed in a dosette in its unopened blister pack.

What if a NOAC dose is missed? If a day’s dose is missed, the next day’s dose should not be doubled. If a NOAC is taken because of AF and a dose is missed, continue at the usual dose starting with the next scheduled dose. However, if patients are taking rivaroxaban twice-daily during the
first 3 weeks after VTE, a missed morning dose should be taken as soon as possible so that 2 of the 15 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 NOACs around the time of the procedure; consideration can also be given to the use of the pro-hemostatic tranexamic acid mouthwash before and after the procedure. 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 the Clinical Guide: New/Novel Oral Anticoagulants (NOACs): Peri-Operative Management.

**What if the patient has a prosthetic heart valve?** In patients with a mechanical heart valve, NOACs are contraindicated. In patients with a bioprosthetic (tissue) heart valve, NOACs may be used but this has not been formally studied.

**NOACs and other medications:**

**Can an NSAID be taken with NOACs?** In general, long-term use of a non-steroidal anti-inflammatory drug (NSAID) combined with a NOAC should be avoided. It is probably safe to combine an NSAID with a NOAC for short, 3-5 day periods, for example, to treat acute joint pain. Acetaminophen is preferred over an NSAID for joint pain, headache or for cold or flu-like symptoms. If there is a need for longer periods of treatment with an NSAID or acetaminophen, this warrants a specific discussion between the patient and 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.** If one of these drugs is medically indicated over an extended duration, an alternative to a NOAC 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 NOAC?** Patients should avoid taking St. John’s Wort if they are taking a NOAC. There are no known restrictions for other herbal medications.

**Table 1: Comparison of key properties of NOACs**

<table>
<thead>
<tr>
<th>Clinical Indications and Doses</th>
<th><strong>DABIGATRAN (Pradaxa®)</strong></th>
<th><strong>RIVAROXABAN (Xarelto®)</strong></th>
<th><strong>APIXABAN (Eliquis®)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation (indefinite duration)</td>
<td>150 mg or 110 mg twice daily</td>
<td>20 mg daily</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>Acute VTE (3 to 6 months)</td>
<td>150 mg twice daily</td>
<td>20 mg daily (15 mg twice daily for initial 21 days)</td>
<td>5 mg twice daily (10 mg twice daily for initial 7 days)</td>
</tr>
<tr>
<td>VTE prevention after knee or hip replacement surgery (14 to 30 days)</td>
<td>110 mg (initial dose) then 220 mg daily</td>
<td>10 mg daily</td>
<td>2.5 mg twice daily</td>
</tr>
</tbody>
</table>

**Key Pharmacologic Properties**
### Mechanism of action

- **Dabigatran (Pradaxa®)**: Direct factor IIa (thrombin) inhibitor
- **Rivaroxaban (Xarelto®)**: Direct factor Xa inhibitor
- **Apixaban (Eliquis®)**: Direct factor Xa inhibitor

### Renal clearance

- **Dabigatran (Pradaxa®)**: 80%
- **Rivaroxaban (Xarelto®)**: 33% (active drug)
- **Apixaban (Eliquis®)**: 25%

### Half-life:

- **Normal to mild impairment (CrCl ≥50 mL/min)**: 7-17 hours
- **Moderate renal impairment (CrCl 30-49 mL/min)**: 17-20 hours
- **Severe renal impairment (CrCl <30 mL/min)**: 21-35 hours

### Onset of action (after oral intake)

- **Dabigatran (Pradaxa®)**: 1-3 hours
- **Rivaroxaban (Xarelto®)**: 1-3 hours
- **Apixaban (Eliquis®)**: 1-3 hours

### Key Practical Properties

#### Food or alcohol interactions
- **Dabigatran (Pradaxa®)**: none
- **Rivaroxaban (Xarelto®)**: none
- **Apixaban (Eliquis®)**: none

#### Drug interactions
- **Dabigatran (Pradaxa®)**: amiodarone, quinidine, azole antifungals (e.g. ketoconazole), rifampin increase dabigatran levels
- **Rivaroxaban (Xarelto®)**: azole antifungals (e.g. ketoconazole), rifampin increase rivaroxaban levels
- **Apixaban (Eliquis®)**: azole antifungals (e.g. ketoconazole), rifampin increase apixaban levels

#### Antidote
- **Dabigatran (Pradaxa®)**: Idarucizumab
- **Rivaroxaban (Xarelto®)**: none to date
- **Apixaban (Eliquis®)**: none to date

#### Laboratory Measurement of Anticoagulant Effect

- **Dabigatran (Pradaxa®)**: aPTT or thrombin clotting time (TCT)
- **Rivaroxaban (Xarelto®)**: prothrombin time (PT)/INR
- **Apixaban (Eliquis®)**: PT/INR

‡Laboratory tests may not reliably reflect levels of anticoagulation with NOACs (See the Clinical Guide: New/Novel Oral Anticoagulants (NOACs): Coagulation Tests).

**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 of thromboembolism and bleeding complications and to assess 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 patient 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 INR or 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 also the Clinical Guides: New/Novel Oral Anticoagulants (NOACs): Coagulation Tests and New/Novel Oral Anticoagulants (NOACs): Peri-Operative Management).

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

How does one switch from warfarin to a NOAC? After stopping warfarin, the patient 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 rapid (peak effect 1-3 hours after ingestion). 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.

**ACUTE MEDICAL EMERGENCIES IN PATIENTS RECEIVING A NOAC:**

What if my patient has an acute ischemic stroke? In patients who have an acute stroke and are receiving a NOAC, the management should be similar to other patients with an ischemic stroke. In general, compliance with the NOAC should be assessed. Where appropriate, thrombolytic therapy should be considered, especially if sufficient time has elapsed since the last NOAC dose (i.e. 12-18 hours) so there is little residual anticoagulant effect. The addition of an antiplatelet drug should also be considered. 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 similar to other patients with such an event. Consultation with a cardiologist is 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: New/Novel Oral Anticoagulants (NOACs): Management of Bleeding). Consultation with a hematologist or thrombosis specialist is advised in these situations.

**COMPARISON OF NOACS:**

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

Which NOAC 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 NOAC 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 NOACs may be preferable.

**Table 2: Suggested use of NOACs according to patient characteristics for stroke prevention in AF†**

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Suggested NOAC regimen</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AF at high risk for stroke (e.g. CHADS$_2$ ≥ 3) or with prior stroke</td>
<td>dabigatran 150 mg twice daily</td>
<td>This dose of dabigatran conferred the greatest risk reduction in stroke compared with warfarin</td>
</tr>
<tr>
<td></td>
<td>rivaroxaban 20 mg daily</td>
<td>More patients with prior stroke were studied with rivaroxaban</td>
</tr>
<tr>
<td></td>
<td>apixaban 5 mg twice daily</td>
<td>The greatest benefit to prevent stroke compared with warfarin occurred in patients with CHADS$_2$ ≥ 3</td>
</tr>
<tr>
<td>Patients with AF at high risk for bleeding</td>
<td>apixaban 5 mg twice daily</td>
<td>This dose of apixaban conferred a decrease in the risk of major bleeding compared with warfarin</td>
</tr>
<tr>
<td></td>
<td>dabigatran 110 mg twice daily</td>
<td>This dose of dabigatran conferred a decrease in the risk of major bleeding compared with warfarin</td>
</tr>
<tr>
<td>Elderly (≥ 80 years) patients with impaired renal function (e.g. CrCl &lt; 50 mL/min)</td>
<td>apixaban 2.5 mg twice daily</td>
<td>Apixaban was associated with a reduced risk of bleeding in patients with impaired renal function</td>
</tr>
<tr>
<td></td>
<td>rivaroxaban 15 mg once daily</td>
<td>A reduced rivaroxaban dose was studied in patients with impaired renal function</td>
</tr>
</tbody>
</table>

†Alternative options may also be reasonable. 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.

**Which NOAC 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 NOACs for the treatment of acute VTE.

**How should NOACs be used in patients with impaired renal function?** The NOACs differ in terms of how they should be used in patients who have impaired renal function. Table 3 provides a suggested guide for using NOACs in patients with impaired renal function.
### TABLE 3: SUGGESTED USE OF NOACS ACCORDING TO PATIENT RENAL FUNCTION FOR STROKE PREVENTION IN AF†

<table>
<thead>
<tr>
<th>NOAC</th>
<th>CrCl (mL/min)</th>
<th>DRUG DOSE</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>≥ 50</td>
<td>110 or 150 mg twice daily</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>30-49</td>
<td>110 or 150 mg twice daily</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>&lt; 30</td>
<td>Avoid dabigatran</td>
<td>Consider warfarin as alternative anticoagulant</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>≥ 50</td>
<td>20 mg daily</td>
<td>Measure CrCl every 12 months</td>
</tr>
<tr>
<td></td>
<td>30-49</td>
<td>15 mg daily</td>
<td>Measure CrCl every 6 months and with acute illness Consider avoiding if deteriorating renal function</td>
</tr>
<tr>
<td></td>
<td>&lt; 30</td>
<td>Avoid rivaroxaban</td>
<td>Consider warfarin as alternative anticoagulant</td>
</tr>
<tr>
<td>Apixaban</td>
<td>≥ 50</td>
<td>5 mg twice daily</td>
<td>Measure CrCl every 12 months</td>
</tr>
<tr>
<td></td>
<td>25-49</td>
<td>5 mg twice daily</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>15-24</td>
<td>No dose recommendations can be made</td>
<td>Very limited clinical data with apixaban Consider warfarin as alternative anticoagulant</td>
</tr>
<tr>
<td></td>
<td>&lt; 15</td>
<td>Avoid apixaban</td>
<td>Consider warfarin as alternative anticoagulant</td>
</tr>
</tbody>
</table>

†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 GUIDES:

- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis (DVT): Treatment
- New/Novel Oral Anticoagulants (NOACs): Coagulation Tests
- New/Novel Oral Anticoagulants (NOACs): Management of Bleeding
- New/Novel Oral Anticoagulants (NOACs): Peri-Operative Management
- 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
REFERENCES:


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