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Use of Non-Vitamin K Antagonist Oral Anticoagulants (NOAC) in Non-Valvular Atrial Fibrillation

Effective Date: April 1, 2015
Revised Date: November 12, 2015

Scope

This guideline provides recommendations for the use of non-vitamin K antagonist oral anticoagulants (NOAC)* in the prevention of stroke and systemic embolism in adults aged ≥19 years with non-valvular atrial fibrillation. Description and comparison of the characteristics and indications of NOACs will be provided. The use of NOACs in orthopedic prophylaxis and venous thromboembolism treatment is not included.

This guideline is part of the BCGuidelines.ca – *Stroke and Atrial Fibrillation* series. The series includes three other guidelines: *Atrial Fibrillation – Diagnosis and Management; Stroke and Transient Ischemic Attack – Acute and Long-Term Management;* and *Warfarin Therapy Management*.

Key Recommendations

- Non-vitamin K antagonist oral anticoagulants (NOACs) are a class of anticoagulants each with distinct pharmacologic characteristics and should **not** be considered interchangeable.
- NOACs can be considered for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in whom anticoagulation is indicated.
- Renal function should be checked prior to starting a NOAC and then periodically depending on clinical status.
- Check for potential drug interactions that may increase or decrease the drug levels of the NOAC and consider alternative therapy if any significant interaction is present.
- Choice of agent for an individual patient is based on clinical factors, including the risk for stroke, bleeding history, renal and liver function, warfarin experience, and personal preference.

Definitions

Non-valvular atrial fibrillation (AF) is defined as AF that occurs in **absence** of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

Non-vitamin K antagonist oral anticoagulants (NOACs) are a class of drugs that directly inhibits the activity of specific "targeted" coagulation factors.[1] The NOACs currently available in Canada (i.e., dabigatran, rivaroxaban, apixaban) are designed to target thrombin (direct thrombin inhibitors) or activated factor X (FXa). By inhibiting the action of these key enzymes in the coagulation cascade, these drugs have potent anticoagulant properties.[2] In contrast, the traditional anticoagulants, namely heparin, low molecular weight heparin and warfarin, are indirect inhibitors that block multiple coagulation factors.

* *Formerly known as NOAC for novel oral anticoagulant and also known as direct oral anticoagulants.*

▶ Characteristics and Pharmacological Properties

NOACs share similar clinical characteristics but they each have unique pharmacological profiles that determine their safety and suitability in individual patients.[3,4] Table 1 summarizes the important properties of NOACs relevant to clinicians. The major practical advantage of the NOACs over warfarin is their predictable pharmacokinetic and pharmacodynamic properties (relative to warfarin), which allow these drugs to be given once or twice daily by mouth in fixed doses. They also have a rapid onset of action, reaching peak plasma concentrations in less than 3 – 4 hours. They have variable half-lives that are highly dependent on renal and/or liver function.

Table 1. Characteristics of non-vitamin K antagonist oral anticoagulants (NOACs)

Characteristic	Dabigatran	Rivaroxaban	Apixaban
Target	Thrombin	FXa	FXa
Peak plasma levels	1 – 2 h*	2 – 4 h	3 – 4 h
Dosing in AF**	Twice daily	Once daily	Twice daily
Must take with food	No	Yes	No
Renal clearance of active drug	80%	33%	25%
Half-life elimination with normal renal function	12 – 18 h	5 – 13 h	12 – 15 h
Dose adjustment in moderate liver impairment	No	Contraindicated	No
Significant drug interactions***	P-gp inhibitors or inducers	P-gp/CYP 3A4 inhibitors or inducers	P-gp/CYP 3A4 inhibitors or inducers

Abbreviations: AF = atrial fibrillation; CYP3A4 = cytochrome P450 3A4 isoenzymes; FXa = activated factor X; h = hours; P-gp = P-glycoprotein.
Footnotes: * Dabigatran action onset may be delayed 2 hours by food.
** Potential variation exists in drug metabolism by different ethnic groups (i.e., lower dose may be indicated in Japanese). Further detailed dosing information found *in Appendix A: Prescription Medication Table for Direct Oral Anticoagulants.*
*** See *Appendix A: Potential NOAC Drug Interactions* for more information about drug interactions.

The NOACs have fewer identified drug interactions compared to warfarin. However, they should either not be given, or should be co-administered with caution, to patients who are also receiving potent inhibitors or inducers of P-glycoprotein (P-gp) transport or cytochrome P450 3A4 isoenzymes (CYP3A4) pathways. *Appendix A: Potential NOAC Drug Interactions* provides a list of some commonly used drugs that interact with NOACs. This is not an exhaustive list and clinically significant drug interactions may be identified with increasing use of these medications.

Management

▶ Evidence for NOAC in Stroke Prevention in Non-Valvular Atrial Fibrillation

The three NOACs currently available in Canada are dabigatran, rivaroxaban and apixaban.

All three have been compared with warfarin in large, multinational, randomized controlled trials in preventing stroke and systemic embolism in patients with non-valvular AF.[5-8] These drugs have been shown to be "no worse" or better than warfarin in preventing stroke or systemic embolism. Consequently, warfarin is still a reasonable alternative in most patients. All three NOACs have been shown to be associated with a lower risk of intracranial bleed. The details of the trial outcomes can be found in *Appendix B: Outcomes from Anticoagulant Active-Comparison Randomized Controlled Trials*. It is important to note that the absolute differences of these outcome events between a NOAC and warfarin are approximately 0.5% or less. Cost-effectiveness analyses are very sensitive to the specific patient population (e.g., age, warfarin control) and drug cost, and are not helpful in making therapeutic decisions in an individual patient.

Table 2. NOACs versus warfarin for prevention of stroke or systemic embolism in non-valvular atrial fibrillation

Outcomes	Dabig atran 110 mg twice daily	Dabigatran 150 mg twice daily	Rivaroxaban 20 mg once daily	Apixaban 5 mg twice daily
Stroke or systemic embolism prevention	↔*	↓*	↔*	↓*
Major bleeding	↓*	↔	↔	↓*
Intracranial hemorrhage	↓*	↓*	↓*	↓*
Mortality	↔	↔	↔	↓

Footnotes: ↔ no worse than warfarin; ↓ lower risk than warfarin; * result is statistically significant.

How to Choose the Most Appropriate NOAC for Your Patient

There is no single "best" or "first choice" NOAC as the different NOACs have not been compared in a head-to-head fashion and the clinical trials to date were not designed to help select the most appropriate anticoagulant in individual patients. The drug selection process requires a systematic approach that incorporates: understanding the clinical trials data, consideration of the risk factors for bleeding, checking the patients' recent renal and liver function, reviewing potential drug interactions, talking to the patient about his/her values, life style (e.g., accessibility to International Normalized Ratio (INR) monitoring), drug cost, and educating them about the limitations and advantages of the options. See *Appendix C: Prescription Medication Table for Non-Vitamin K Antagonist Oral Anticoagulants (NOAC) with Non-Valvular Atrial Fibrillation* for drug costs and doses.

Contraindications to NOACs

There are selected patient populations in whom NOACs should NOT be used because of a specific safety concern or lack of evidence. NOACs should not be used and warfarin is recommended in patients with any of the following features:

- Mechanical heart valve[9];
- Valvular atrial fibrillation (i.e., mitral stenosis, bioprosthetic heart valve or mitrial valve repair);
- Severe renal impairment with creatinine clearance (CrCl) < 30 mL/min;
- Severe liver dysfunction (link to calculator: Child-Pugh grade C);
- Pregnant women (low molecular weight heparin is preferred – see BCGuidelines.ca – *Warfarin Therapy Management*) or breast-feeding mothers; and/or
- Need to take a potent P-gp or CYP3A4 inhibitors or inducers (see *Appendix A: Potential NOAC Drug Interactions*).

In patients weighing less than 60 kg or greater than 100 kg, calculate the creatinine clearance (CrCl) and do not depend on the estimated glomerular filtration rate (eGFR) provided by laboratory reports (because weight has not be adjusted). CrCl can be calculated using the (link to calculator: Cockcroft-Gault formula) according to the patient's age, weight, and serum creatinine:

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{Weight (kg)} \times 1.04 \text{ if female or } 1.23 \text{ if male}}{\text{Serum creatinine (micromol/L)}}$$

Coagulation Testing

The INR and the activated partial thromboplastin time (aPTT) are used to monitor the anticoagulant effects of warfarin and heparin, respectively. They should NOT be used to measure the anticoagulant effects of NOACs.[10,11] Depending on the laboratory reagent used and the timing of the blood draw after a dose of NOAC, the INR and aPTT may or may not be prolonged. Consequently, these tests should **not** be used to estimate the anticoagulant activity.[12] It is reasonable to assume that some anticoagulant activity is present if either the INR and/or aPTT is elevated, but it is **not** appropriate to assume that anticoagulant activity is **absent** if these tests are within the normal range, especially if the last dose of a NOAC was taken within the prior 24 to 48 hours.

Thrombin time (TT) is a highly sensitive assay to the presence of a direct thrombin inhibitor.[13] It will be elevated in patients treated with dabigatran. If the TT is normal, it excludes the presence of any anticoagulant effect from dabigatran. Although it might be helpful in patients presenting with bleeding to determine if dabigatran is present, it should not be used routinely to measure or monitor the anticoagulant effect of dabigatran.

Specific assays, including the dilute thrombin time test (e.g., Hemoclot® assay)[14,15] and anti-FXa assay,[16] that measure the indirect anticoagulant activities of NOACs have not been evaluated for clinical use and those commercially available have not been standardized or validated.

New Starts (Warfarin Naïve Patients)

Table 3 compares some of the advantages and disadvantages of warfarin compared to the NOACs. Both the clinician and patient should carefully consider these reasons in addition to the evidence from clinical trials. Patients **must** have their renal function checked prior to starting a NOAC.

Table 3. Advantages and disadvantages of warfarin versus NOACs

Favours Warfarin	Favours NOAC
• Inexpensive	• Convenience
• Prone to skipping doses (e.g., dementia)	• Prone to skipping laboratory testing
• Drug interaction with P-gp/CYP3A4	• Poor venous access or lab access
• Renal impairment (CrCl < 30 mL/min)	• Variable diet or frequent alcohol use
• History of GI bleed	• History of intracranial bleed
• Also needs ASA or other antiplatelet therapy	
• Extremes of body weight (< 40 kg or > 120 kg)	
• Lack of long-term toxicity data for NOAC	
• Reversal agents available	

Abbreviations: ASA = acetyl-salicylic acid; CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4 isoenzymes; GI = gastrointestinal; kg = kilogram; mL/min = milliliter per minute; NOAC = non-vitamin K antagonist oral anticoagulants; P-gp = P-glycoprotein.

Patients Already on Warfarin

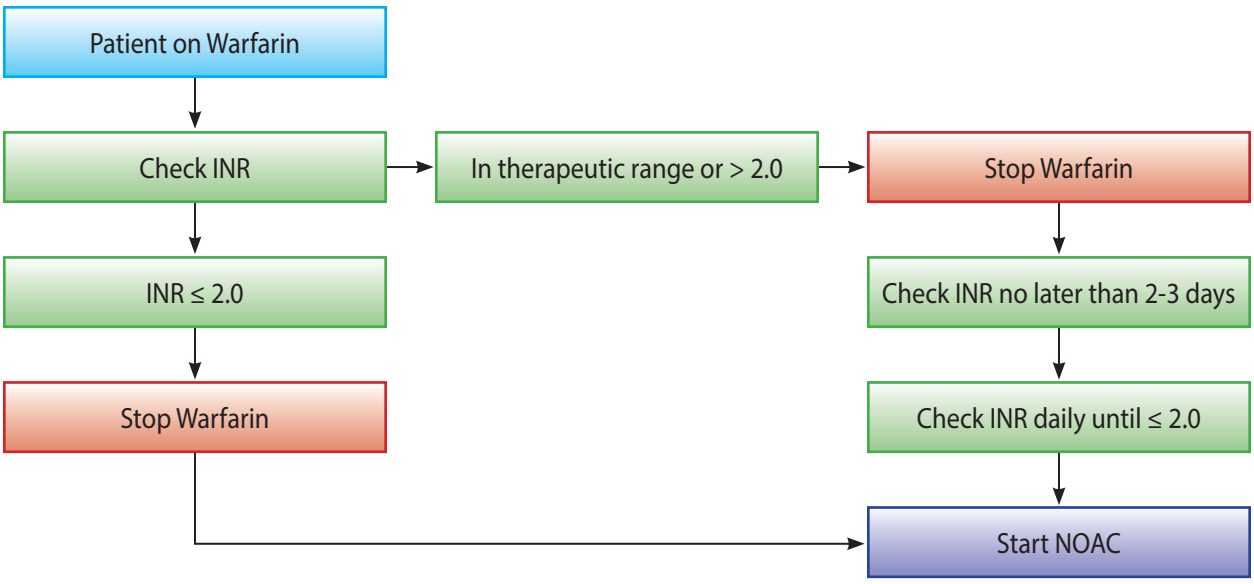
Patients who are already anticoagulated with warfarin at a stable dose and maintain optimal time in therapeutic range (TTR) are unlikely to receive a morbidity or mortality benefit from switching to a NOAC.[18-20]

TTR is a measure of the proportion of total treatment time that the INR is within the therapeutic range (INR 2.0 – 3.0). Most experts agree that the optimal or acceptable TTR is 65% or higher.[21-23] In those patients who have had difficulty maintaining the TTR above 65% or have demonstrated labile INRs, switching to NOAC should be considered provided that the patient does not have contraindications to using a NOAC, such as drug interaction or severe renal impairment.

Switching Between Warfarin and NOAC

If switching is required, there are no standard strategies for safe switching. In clinical trials, this transition period is associated with an increased risk of stroke and systemic embolism.[24] Figure 1 provides a reasonable approach to switching from warfarin to a NOAC.

Figure 1. Switching from warfarin to a NOAC



Switching from a NOAC to warfarin is more complicated because NOACs can increase the baseline INR. If a patient is on a NOAC:

1) Start warfarin preferably by using an induction nomogram (see BCGuidelines.ca – *Warfarin Therapy Management*).
2) Continue the NOAC (overlap is needed because warfarin is not effective for at least 5 days).
3) After the first 2 doses of warfarin, check the INR and continue to check the INR as needed (every 1 – 3 days) until the INR is 2.5 or higher.
4) Once the INR is 2.5 or higher, stop the NOAC. Continue Warfarin and repeat the INR again in 2 days to ensure that the true INR is therapeutic above 2.0.
5) Always check the INR before the next dose of the NOAC so that the NOAC level is at its lowest and is least likely to influence the INR.

Ongoing Care

Patient Follow-Up

Patients who choose to use NOAC should be reassessed for the first time within 1 month after starting a NOAC to review potential side effects, such as gastrointestinal (GI) upset or excessive bruising or bleeding. The frequency of follow-up thereafter should be individualized based on bleeding risk. Medication compliance and education regarding signs and symptoms of stroke and bleeding should be reviewed with the patient periodically to maximize adherence. Because the half-lives of NOACs are relatively short, missing 1 – 2 doses of the medication can lead to subtherapeutic coverage. Patients should be encouraged to use a pill tracking system (e.g., dosette, blister pack) to maximize compliance. Note: dabigatran **must be** stored in its original bottle or blister package to protect from moisture. Once the bottle is opened, capsules must be used within 60 days. Mishandling and storage can cause the drug to become ineffective.[25]

Renal function testing should be done before starting NOAC and at least once every 6 – 12 months, or more frequently if clinically indicated (e.g., elderly patient with borderline renal function).

Temporary Interruption of NOAC

Although clinical trials evidence is not available, there are consensus recommendations and manufacturer suggestions on when to temporarily discontinue NOAC in preparation for surgery or other invasive procedures.[26-29] It is important to note that clinical trials evidence for management of warfarin in the perioperative setting are also sparse and standard of practice is largely based on clinical experience.[30-32]

The timing of interruption and resumption of NOAC in the perioperative period aims to balance the competing risks of bleeding and thrombosis. Without reliable laboratory testing to measure the anticoagulant effect, the timing of the last dose of NOAC depends on drug half-life, renal function and the bleeding risk associated with the procedure. This must be balanced against the risk of stroke, which increases as the interruption period prolongs.

Table 4 provides recommendations on how long to withhold a NOAC based on the drug's pharmacokinetic properties, a patient's renal function, and the estimated risk of bleeding associated with the procedure. The risk of stroke based on the patient's $CHADS_2$ score helps to determine if bridging is indicated in those on warfarin (see BCGuidelines.ca – *Warfarin Therapy – Management During Invasive Procedures and Surgery*), but bridging practice has not been advocated by experts in patients stopping NOACs for procedures and surgery.

Table 4. NOAC withholding period prior to procedure[26]

NOAC	Renal function (CrCl, ml/min)	Half-life (hr)	Number of skipped doses before day of surgery:	
			Standard risk for bleeding	High risk for bleeding
dabigatran	> 50	12 – 18	2	4
dabigatran	30 to 50	13 – 23	4	8
rivaroxaban	> 30	7 – 13	1	2
apixaban	> 30	7 – 13	2	4

Abbreviations: CrCl = creatinine clearance; hr = hour(s); ml/min = milliliter per minute; NOAC = non-vitamin K antagonist oral anticoagulants.

See *Appendix D*: *Relative Risk of Bleeding Associated with Common Invasive Procedures* for listing of procedures and their associated risk of bleeding.[20,33]

These recommendations should be modified individually, if indicated, and should be discussed with the surgeon or interventionalist, and anesthesiologist involved. Patients having neuraxial blockade (spinal anesthesia or epidural analgesia) are considered to have a very high risk of bleeding because of the rare but devastating complication of spinal hematoma. Similar to warfarin, withholding NOACs for minor procedures (e.g., skin biopsy, cataracts or dental procedures) is not necessary.

After the procedure or surgery, NOAC should not be restarted within the first 24 – 48 hours because therapeutic levels are reached within 3 – 4 hours of the first dose. The timing of the first dose should be discussed with the surgeon or interventionalist. In patients who require venous thromboembolism (VTE) prophylaxis, low molecular weight heparin can be given prior to restarting NOAC. No overlapping is necessary in switching from low molecular weight heparin to NOAC. In patients undergoing major joint replacement where prophylactic doses of NOAC is used post-operatively, the therapeutic dose of NOAC for atrial fibrillation can be introduced when the surgeon is satisfied with hemostasis.

▶ Management of Bleeding

Specific antidotes are currently not available for NOACs in Canada.[34,35] Idarucizumab has been approved in the United States for reversal of dabigatran. Andexanet, a reversal agent for FXa inhibitors (e.g., rivaroxaban, apixaban, low molecular weight heparin), is in clinical trial testing. Usual supportive care with fluid support, red cell transfusion, etc. should be done and the source of bleeding must be identified and treated if possible. Frozen plasma has no role in reversing the anticoagulant effects of NOACs. The use of prothrombin complex concentrate and recombinant activated factor VII have not been adequately evaluated and should not be routinely given to patients presenting with bleeding while on NOACs. Their use in life-threatening cases should be discussed with an expert on the use of blood products and anticoagulants (e.g., hematologist, transfusion medicine specialists). The risk of thrombosis is a serious complication with these blood products, especially in patients who are already at risk for stroke. Dialysis is useful in removing ~60% of dabigatran and can be considered in cases of overdose or severe renal failure. Dialysis is not effective for removing rivaroxaban or apixaban because they are tightly protein bound.

Resources

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▶ Resources

- BC Guidelines, www.BCGuidelines.ca – *Warfarin Therapy – Management During Invasive Procedures and Surgery*
- Heart and Stroke Foundation – British Columbia and Yukon, www.heartandstroke.bc.ca
- Thrombosis Canada, thrombosiscanada.ca
- HealthLinkBC, www.healthlinkbc.ca or by telephone (toll free in BC) 8-1-1 or 7-1-1 (for the hearing impaired) for health information, translation services and dieticians.
- Rapid Access to Consultative Expertise (RACE), www.raceconnect.ca or by telephone 604-696-2131, toll free 1-877-696-2131, program designed to increase family physician access to specialist consultation.
- PharmaCare Special Authority, www.health.gov.bc.ca/pharmacare/sa/saindex.html#list, provides benefit status for medication coverage and specific medical circumstances of coverage depending on BC PharmaCare plan rules.

▶ Appendices

- Appendix A: Potential NOAC Drug Interactions
- Appendix B: Outcomes from Anticoagulant Active-Comparison, Randomized Controlled Trials (as reported)
- Appendix C: Prescription Medication Table for Non-Vitamin K Antagonist Oral Anticoagulants (NOAC) with Non-Valvular Atrial Fibrillation
- Appendix D: Relative Risk of Bleeding Associated with Common Invasive Procedures

▶ Associated Documents

The following documents accompany this guideline:

- BCGuidelines.ca – *Stroke and Transient Ischemic Attack – Acute and Long-Term Management*
- BCGuidelines.ca – *Atrial Fibrillation – Diagnosis and Management*
- BCGuidelines.ca – *Warfarin Therapy Management*
- 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.

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: Potential NOAC Drug Interactions

<table>
<tr><th>Dabigatran[1–3]</th><th>Apixaban[4–6] and Rivaroxaban[7–9]</th></tr>
<tr><td colspan="2">Contraindicated
Note: Effect may last for several weeks after discontinuation of inducers of P-glycoprotein and/or CYP3A4</td></tr>
<tr><td colspan="2">Anticoagulants
anti-thrombin agents (e.g., bivalirudin)
Factor-Xa inhibitors (e.g., apixaban and rivaroxaban)
heparin (unless used to maintain a patent central venous or arterial catheter)
heparin derivatives (e.g., fondaparinux)
low molecular weight heparins (e.g., dalteparin and enoxaparin)
warfarin (unless switching to or from a NOAC)</td></tr>
<tr><td>Strong inhibitors of P-glycoprotein
azole-antimycotics (e.g., itraconazole, ketoconazole, posaconazole, and voriconazole)
HIV protease inhibitors (e.g., darunavir fosamprenavir, indinavir, lopinavir nelfinavir, ritonavir, and saquinavir)</td><td>Strong inhibitors of both P-glycoprotein and CYP3A4
azole-antimycotics (e.g., itraconazole, ketoconazole, posaconazole, and voriconazole)
boceprevir
cobicistat
HIV protease inhibitors (e.g., darunavir fosamprenavir, indinavir, lopinavir nelfinavir, ritonavir, and saquinavir)
imatnib</td></tr>
<tr><td colspan="2">Avoid use
Note: Effect may last for several weeks after discontinuation of inducers of P-glycoprotein and/or CYP3A4</td></tr>
<tr><td colspan="2">Platelet inhibitors
ASA, clopidogrel, dipyridamole, prasugrel, sulfinpyrazone, ticagrelor, ticlopidine</td></tr>
<tr><td>Moderate inhibitors of P-glycoprotein
cyclosporine
dronedarone
itraconazole posaconazole
tacrolimus
ticagrelor</td><td></td></tr>
<tr><td rowspan="2">Strong inducers of P-glycoprotein
carbamazepine
dexamethasone
doxorubicin
nefazodone
phenobarbital
phenytoin
prazocin
rifampin
St. John's Wort
tenofovir
tipranavir
trazodone
vinblastine</td><td>Strong inducers of CYP3A4
bosentan
efavirenz
etravirine
fosphenytoin
nafcillin
nevirapine
oxcarbazapine
phenobarbital
primidone
rifabutin</td></tr>
<tr><td>Inducers of P-glycoprotein
doxorubicin
prazocin
tipranavir
trazodone
vinblastine</td></tr>
</table>

<table>
<tr><th>Dabigatran[1–3]</th><th>Apixaban[4–6] and Rivaroxaban[7–9]</th></tr>
<tr><td colspan="2">Use With Caution</td></tr>
<tr><td colspan="2">Nonsteroidal anti-inflammatory drugs (NSAIDs)
• Diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac</td></tr>
<tr><td>Other inhibitors of P-glycoprotein
Notes:
1) Use with caution in patients with normal renal function.
2) Avoid use in patient with CrCl < 50 mL/min or age ≥ 80 years.
3) Where concomitant use cannot be avoided, administer dabigatran at least 2 hours before P-glycoprotein inhibitor.
• abiraterone
• alfentanil
• amiodarone
• atorvastatin
• azithromycin
• beceprevir
• carvedilol
• clarithromycin
• cobicistat
• diltiazem
• dipyridamole
• duloxetine
• erythromycin
• fenofibrate
• grapefruit (fruit or juice)
• ivacaftor
• lovastatin
• mefloquine
• nicardipine
• nifedipine
• progesterone
• propafenone
• propranolol
• quinidine
• quinine
• sunitinib
• tamoxifen
• ticagrelor
• tolvaptan
• ulipristal
• verapamil</td><td>Inhibitors of P-glycoprotein and/or CYP3A4
Notes:
1) Use with caution in patients with normal renal function.
2) Avoid use in patient with CrCl < 30 mL/min or age > 80 years or weight < 60 kg.
• amiodarone
• azithromycin
• cimetidine
• clarithromycin
• cyclosporine
• diltiazem
• donedarone
• erythromycin
• felodipine
• fluconazole
• grapefruit (fruit or juice)
• lapatinib
• nicardipine
• quinidine
• tamoxifen
• ticagrelor
• verapamil</td></tr>
<tr><td colspan="2">Gastric pH-elevating agents
Note: Where concomitant use cannot be avoided, administer dabigatran at least 2 hours before.
• proton pump inhibitors (e.g., esomprazole, omeprazole, pantoprazole, and rabeprazole)
• H_2-antagonists (e.g., cimetidine, famotidine, and ranitidine)
• antacids (aluminium compounds, sodium bicarbonate, calcium and/or magnesium compounds, or combinations of these)</td></tr>
</table>

Abbreviations: ASA = acetyl-salicylic acid; CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4 isoenzymes; HIV = human immunodeficiency virus; kg = kilogram; mL/min = milliliter per minute; NOAC = non-vitamin K antagonist oral anticoagulants.

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Appendix B: Outcomes from Anticoagulant Active-Comparison, Randomized Controlled Trials (as reported)

The **absence of direct comparisons** between the new oral anticoagulants and the **heterogeneity** of the three principal randomized controlled trials (RCTs) limits reaching firm conclusions regarding differences between the new oral anticoagulants.[1-4] **Methodologic limitations** have increased relevance as sources of potential bias in non-inferiority RCTs.[5]

	Dabigatran (RE-LY)[6,7]		Rivaroxaban (ROCKET AF)[2,8,9]	Apixaban (ARISTOTLE)[10]
	D110 versus WARF	**D150 versus WARF**	**RIVA versus WARF**	**APIX versus WARF**
Primary composite outcome				
stroke or systemic embolism[i]	D110 1.54% per year WARF 1.71% per year **0.90 (0.74, 1.10)**	D150 1.11% per year WARF 1.71% per year **0.65 (0.52, 0.81)** **↓ 0.60% per year**	RIVA 2.1% per year WARF 2.4% per year **0.88 (0.75, 1.03)**	APIX 1.27% per year WARF 1.60% per year **0.79 (0.66, 0.95)** **↓ 0.33% per year**
Secondary outcomes[ii]				
total mortality	D110 3.75% per year WARF 4.13% per year **0.91 (0.80, 1.03)**	D150 3.64% per year WARF 4.13% per year **0.88 (0.77, 1.00)**	RIVA 4.5% per year WARF 4.9% per year **0.92 (0.82, 1.03)**	APIX 3.52% per year WARF 3.94% per year **0.89 (0.80, 1.00)** vital status missing for 380 patients
major bleed[iii]	D110 2.87% per year WARF 3.57% per year **0.80 (0.70, 0.93)** **↓ 0.70% per year**	D150 3.32% per year WARF 3.57% per year **0.93 (0.81, 1.07)**	RIVA 3.6% per year WARF 3.4% per year **1.03 (0.89, 1.19)***	APIX 2.13% per year WARF 3.09% per year **0.69 (0.60, 0.80)*** **↓ 0.96% per year**
intracranial hemorrhage[iv]	D110 0.23% per year WARF 0.76% per year **0.30 (0.19, 0.45)** **↓ 0.53% per year**	D150 0.32% per year WARF 0.76% per year **0.41 (0.28, 0.60)** **↓ 0.44% per year**	RIVA 0.5% per year WARF 0.7% per year **0.67 (0.47, 0.93)*** **↓ 0.2% per year**	APIX 0.33% per year WARF 0.80% per year **0.42 (0.30, 0.58)*** **↓ 0.47% per year**
major gastrointestinal bleed	D110 1.15% per year WARF 1.07% per year **1.08 (0.85, 1.38)**	D150 1.56% per year WARF 1.07% per year **1.48 (1.18, 1.85)** **↑ 0.49% per year**	RIVA 2.00% per year WARF 1.24% per year **1.61 (1.30, 1.99)*** **↑ 0.76% per year**	APIX 0.76% per year WARF 0.86% per year **0.89 (0.70, 1.15)***

Abbreviations: D110 = dabigatran 110 mg PO BID; D150 = dabigatran 150 mg PO BID; RIVA = rivaroxaban 20 mg (15 mg) PO daily; APIX = apixaban 5 mg (2.5 mg) PO BID; WARF = adjusted-dose warfarin PO daily.
black bolded values = relative risk with 95% confidence interval; **blue bolded values** = absolute risk reduction or increase if statistically significant; *truncated follow-up: events occurring 2 days after treatment discontinuation were not counted.

Notes:

i Includes ischemic stroke, hemorrhagic stroke, unclassified stroke, or non-CNS systemic embolism; 2013 therapeutic review judged the event definitions to be similar between the RCTs.[1]

ii Appropriate methodology for statistical significance testing of secondary outcomes in non-inferiority RCTs is uncertain.[11]

iii Includes decrease Hb ≥ 20 g/L, ≥ 2 unit transfusion whole blood or packed cells, bleed in a critical site, or fatal outcome; 2013 therapeutic review judged the event definitions to be similar between the RCTs;1 2012 Ontario population-based cohort study, 125 195 adults aged ≥ 66 with atrial fibrillation prescribed warfarin, found a major bleed rate of 3.8% per person-year.[12]

iv Includes hemorrhagic stroke and other intracranial bleeds; 2012 Ontario population-based cohort study, 125 195 adults aged ≥ 66 with atrial fibrillation prescribed warfarin, found an intracranial hemorrhage rate of 0.2% per person-year.[12]

Additional Comments:

1. Increase in stroke or systemic embolism after discontinuation of study drug: US FDA medical reviews noted excess stroke and systemic embolism in participants receiving rivaroxaban and apixaban compared with warfarin during the observation period when patients were transitioned off of assigned study drug to usual care (e.g., VKA antagonist) at the end of study.[11,13,14]

2. Myocardial infarction: US FDA medical review noted an increased risk of myocardial infarction of 0.2% per year in participants receiving dabigatran compared with warfarin;[15] 2012 meta-analysis (7 RCTs, 30 514 participants, dabigatran vs. various comparators including warfarin), dabigatran increased the risk of myocardial infarction and acute coronary syndrome (OR 1.33, 95% CI 1.03 to 1.71).[16]
3. Syncope: US FDA medical review noted numerically more serious syncopal events (i.e., syncope, vertigo, dizziness, presyncope) in participants receiving apixaban compared with warfarin (apixaban = 1.4%, warfarin = 1.0%).[11]
4. Major bleed events older adults: significant treatment by age interaction for major bleeding in participants receiving dabigatran compared with warfarin (P for interaction < 0.001);[17] older adults aged ≥ 75 dabigatran 110 mg vs. warfarin 1.01 (0.83, 1.23), dabigatran 150 mg vs. warfarin 1.18 (0.98, 1.42).[17]
5. Discontinuations due to adverse events: US FDA medical review noted participants were more likely to discontinue dabigatran due to adverse events compared with warfarin (dabigatran 110 mg = 19%, dabigatran 150 mg = 20.5%, warfarin = 15.7% over the course of the study);[15] gastrointestinal disorders (e.g., dyspepsia, gastrointestinal hemorrhage) were the most common adverse events leading to dabigatran discontinuation.[15]

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Appendix C: Prescription Medication Table for Non-Vitamin K Antagonist Oral Anticoagulants (NOAC) with Non-Valvular Atrial Fibrillation

Generic Name	Trade Name (formulation) (strengths)	Adults Doses	Approximate Cost per 30 days[a]	PharmaCare Coverage[b]
Direct Thrombin Inhibitor[1]				
dabigatran	**Pradaxa®** (capsule) (110, 150 mg)	150 mg BID OR 110 mg BID for patients with ≥ 1 of the following: • Age ≥ 75 years • CrCl 30–50 mL/min • Concurrent use of strong P-glycoprotein inhibitors or platelet inhibitors • Previous GI bleed	$104	Special Authority Limited Coverage
Direct Factor Xa Inhibitors[2,3]				
rivaroxaban	**Xarelto®** (tablet) (15, 20 mg)	20 mg PO once daily with food OR 15 mg PO once daily with food for patients with CrCL 30-49 mL/min	$92	Special Authority Limited Coverage
apixaban	**Eliquis®** (tablet) (2.5, 5 mg)	5 mg PO BID OR 2.5 mg PO BID for patients with ≥ 2 of the following: • Age ≥ 80 years • Body weight ≤ 60 kg • Serum creatinine ≥ 133 µmol/L	$104	Special Authority Limited Coverage

Abbreviations: BID = twice daily; CrCl = creatinine clearance; GI = gastrointestinal; kg = kilogram; µmol/L = micromolar per litre; mg = milligram; mL/min = milliliter per minute; PO = taken orally.

Note: Please review product monographs at hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php and regularly review current Health Canada advisories, warnings and recalls at www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/index_e.html.

Footnotes:

a Pricing is approximate as per PharmaNet 2014/08/20 and does not include dispensing fee.

b PharmaCare coverage is currently limited to patients with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism **AND** in whom anticoagulation is inadequate following at least a 2-month trial of warfarin **OR** for whom anticoagulation using warfarin is contraindicated or not possible due to inability to regularly monitor the patient via International Normalized Ratio (INR) testing (i.e., not access to INR testing services at a laboratory, clinic pharmacy, and at home). PharmaCare Coverage Definitions: **G:** generic(s) are available; **Regular Coverage:** also known as regular benefit; does not require Special Authority. Regular benefits may be fully or partially covered.*; **Limited Coverage:** requires Special Authority for coverage. Limited Coverage benefits approved by Special Authority may be fully or partially covered.*; **RDP**: Reference Drug Program. Drugs included in the RDP are comparable agents of the same therapeutic class. Patients receive full coverage of drugs designated as the Reference Drug(s) of the therapeutic class. Other drugs in the same RDP category are covered up to the price of the Reference Drug; **No coverage:** also known as non-benefit; does not fit the above categories.* Note: Information on which products PharmaCare covers can be obtained using the B.C. PharmaCare Formulary Search (www.health.gov.bc.ca/pharmacare/benefitslookup/). In all cases, coverage is subject to drug price limits set by PharmaCare and to the patient's PharmaCare plan rules and deductibles. See: www.health.gov.bc.ca/pharmacare/plans/index.html and www.health.gov.bc.ca/pharmacare/policy.html for further information.

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3. Bayer Inc. Product monograph Xarelto (rivaroxaban) tablet [Internet]. 2013 [cited 2014 Mar 14].

Appendix D: Relative Risk of Bleeding Associated with Common Invasive Procedures

Risk of Bleeding	Procedure
Very High Risk	• Neurosurgery (intracranial or spinal surgery) • Cardiac surgery (coronary artery bypass or heart valve replacement) • Neuraxial blockade (e.g., epidural)
High Risk	• Major vascular surgery (abdominal aortic aneurysm repair, aortofemoral bypass) • Major urologic surgery (prostatectomy, bladder tumour resection) • Major lower limb orthopaedic surgery (hip/knee joint replacement) • Lung resection surgery • Intestinal anastomosis surgery • Permanent pacemaker insertion or internal defibrillator placement • Colonoscopy with polypectomy or biopsy • Selected procedures (e.g., kidney biopsy, pericardiocentesis)
Intermediate Risk	• Other intra-abdominal surgery • Other intrathoracic surgery • Other orthopaedic surgery • Other vascular surgery • Selected procedures (prostate or cervical biopsy)
Low Risk	• Laparoscopic cholecystectomy • Laparoscopic inguinal hernia repair • Dental procedures • Dermatologic procedures • Ophthalmologic procedures • Coronary angiography • Gastroscopy or colonoscopy without polypectomy or biopsy • Selected procedures (bone marrow or lymph node biopsy, thoracentesis, paracentesis, arthrocentesis)
Very Low Risk	• Single tooth extraction or teeth cleaning • Skin biopsy or selected skin cancer removal • Cataract removal

For more information, see Management Guidelines for Patients Having Elective Invasive Procedures in Medical Imaging:

- Vancouver Coastal Health, Interventional Radiology (under links), website: www.vch.ca/locations-and-services/find-health-services/?program_id=2148
- Fraser Health, Interventional Radiology (under links), website: www.fraserhealth.ca/find-us/services/our-services?program_id=8647

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