



**Pratiques optimales  
de l'AVC au Canada**

# RECOMMANDATIONS CANADIENNES POUR LES PRATIQUES OPTIMALES DE SOINS DE L'AVC

## **Prévention secondaire de l'AVC** **Septième édition, mise à jour 2020**

**Annexe 4 : Anticoagulants oraux visant la prévention de l'AVC chez  
les patients atteints de fibrillation auriculaire**

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## **Annexe 4 : Anticoagulants oraux visant la prévention de l'AVC chez les patients atteints de fibrillation auriculaire**

Ce tableau fournit un résumé des caractéristiques pharmacothérapeutiques, des effets secondaires, des interactions médicamenteuses et d'autres renseignements pour les cinq anticoagulants actuellement utilisés au pays pour la prévention des AVC et de l'embolie systémique dans les cas de fibrillation auriculaire. Il se veut un guide de référence pour les professionnels de la santé qui doivent choisir un médicament pour un patient particulier. La prise de décision doit tenir compte de l'observance du patient, des effets secondaires, des interactions médicamenteuses et du risque hémorragique particulier, en plus des renseignements sur le médicament fournis par le tableau et par d'autres sources.

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Mechanism of Action	Direct Xa inhibitor	Direct thrombin inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Vitamin K antagonism of factors II, VII, IX, X
Stroke Indications	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation Prevention of VTE in THR or TKA Treatment of venous thromboembolic events (DVT and PE).	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation Prevention of VTE in THR or TKR Treatment of venous thromboembolism events (e.g., DVT, PE) and prevention of recurrent DVT and PE	Prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation. Treatment of VTE (DVT and PE) and the prevention of recurrent DVT and PE	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation Prevention of VTE in THR or TKR Treatment of venous thromboembolic events (e.g., DVT, PE) and prevention of recurrent DVT and PE In combination with ASA (75-100mg) for the prevention of stroke, myocardial infarction and cardiovascular death and for the prevention of acute limb ischemia and mortality in patients with coronary artery disease with or without peripheral artery disease	Prophylaxis and/or treatment of VTE, atrial fibrillation with embolization, and as an adjunct in the prophylaxis of systemic embolism after myocardial infarction, including stroke and reinfarction
Active bleeding or significant risk factors for bleeding	Active bleeding or significant risk factors for bleeding Concurrent therapy with Strong CYP 3A4& P-gp inhibitors (e.g., azoles, ritonavir) Moderate to severe hepatic impairment associated with coagulopathy and clinically relevant bleeding risk Pregnant/Breastfeeding Concomitant treatment	Active bleeding or significant risk factors for bleeding <b>CrCl&lt;30 ml/min</b> Concurrent therapy with Strong P-gp inducer (e.g., rifampin) Pregnant/Breastfeeding	Clinically significant active bleeding including GI bleeding. Lesions or conditions at increased risk of clinically significant bleeding, Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Pregnancy/Breastfeeding Concomitant treatment with other anticoagulants.	Active bleeding or significant risk factors for bleeding Concurrent therapy with Strong CYP3A4 & P-gp inhibitors (e.g., azoles, ritonavir) Pregnancy/Breastfeeding Moderate to severe hepatic impairment associated with coagulopathy and clinically relevant bleeding risk	Active bleeding or significant risk factors for bleeding Pregnancy

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
	with other anticoagulants				
<b>Side Effects</b>	Bleeding: Lower risk of bleeding vs. warfarin	Gastritis-like symptoms; dyspepsia, Bleeding: 150 mg BID – similar bleeding risk to warfarin; but higher risk of GI bleed 110 mg BID – lower bleeding risk than warfarin;	Bleeding: Lower risk of bleeding vs warfarin.	Bleeding: Similar risk to warfarin overall. Higher risk of transfusion vs. warfarin. Higher risk of GI bleed vs. warfarin.	Bleeding: Purple toe syndrome (rare)
<b>Landmark Trials</b>	ARISTOTLE NEJM 2011;365:981-92  AVERROES NEJM 2011; 364:806-817.	RE-LY NEJM 2009;361:1139-51	ENGAGE AF-TIMI 48 N Engl J Med; 2013;369:2093-2104	ROCKET-AF NEJM 2011;365:883-91	Multiple RCTs and Meta-Analyses in both valvular and non-valvular Atrial Fibrillation
<b>Inclusion Criteria</b>	Documented AFib or AFlutter plus at least one of: Previous stroke, TIA, systemic embolism Age >75 Heart failure DM HTN requiring treatment	Documented non-valvular Fib within 6 mos and at least 1 of: Previous stroke/TIA Heart failure Age > 75 Age >65 + DM HTN CAD	Documented AFib with a CHADS2 score of 2 or higher and anticoagulation therapy planned for the duration of the trial	Documented non-valvular AFib, <u>with history of stroke, TIA, or systemic embolism</u> or at least 2 of the following: Heart failure HTN Age >75 DM	
<b>Exclusion Criteria</b>	AFib due to reversible cause Moderate or severe valvular disease Stroke in past 7 days CrCl<25 ml/min Need for ASA+clopidogrel or ASA >165 mg/d	Severe heart-valve disorder Stroke within 14 days Severe stroke within 6 months Condition that increased risk of hemorrhage CrCl<30ml/min Active liver disease Pregnancy	AFib due to a reversible disorder; an estimated creatinine clearance of < 30 mL/min; a high risk of bleeding; use of dual antiplatelet therapy; moderate to severe mitral stenosis; other indications for anticoagulation therapy;	Severe heart valve disease TIA caused by reversible disorder Active IE Conditions that increase risk of hemorrhage Uncontrolled HTN Stroke within 14 days or severe stroke within 3 months	

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
		ASA >100 mg/d	acute coronary syndromes, coronary revascularization or stroke within 30 days prior to randomization; and an inability to adhere to study procedures.	Significant liver disease Use of strong CYP 3A4 inhibitors Chronic NSAIDs Pregnancy HIV CrCl<15ml/min ASA >100mg/d	
<b>Primary Outcome Measures: Stroke and Systemic Embolism Event Rate</b>	Stroke/systemic embolism: 1.27%/yr  Stroke: 1.19%/yr Warfarin: 1.51%/yr	Stroke/systemic embolism: 110mg: 1.53% 150mg: 1.11% Warfarin: 1.69%/yr  Stroke: 110mg: 1.44%/yr 150mg: 1.01%/yr Warfarin: 1.57%/yr	Edoxaban 60 mg day vs warfarin  Stroke/systemic embolism: 1.18/yr vs 1.5%/yr	Stroke/systemic embolism: 1.7%/yr Warfarin: 2.2%/yr  Stroke: Not a primary outcome	Stroke/systemic embolism:  ARISTOTLE: 1.60%/yr RE-LY: 1.69%/yr ENGAGE: 1.50%/yr ROCKET-AF: 2.2%/yr  Stroke: ARISTOTLE: 1.51%/yr RE-LY: 1.57%/yr ENGAGE: 1.69%/yr ROCKET-AF: not measured
<b>Overall Bleeding</b>	18.1%/yr	110 mg: 14.6%/yr 150 mg: 16.4%/yr	14.5%/yr	14.9 per 100 pt-yr	RE-LY: 18.2%/yr ROCKET-AF: 14.5 per 100 pt-yr ARISTOTLE: 25.8%/yr ENGAGE: 16.40%/yr
<b>Major Bleeding</b>	2.13%/yr	110 mg: 2.7%/yr 150 mg: 3.1%/yr	2.75%/yr	3.6 per 100 pt-yr	RE-LY: 3.4%/yr ROCKET-AF: 3.4 per 100 pt-yr ARISTOTLE: 3.09%/yr ENGAGE: 3.43%/yr
<b>ICH</b>	0.33%/yr	110 mg: 0.23%/yr 150 mg: 0.30%/yr	0.39%/yr	0.5 per 100 pt-yr	RE-LY: 0.74%/yr ROCKET-AF: 0.7 per 100 pt-yr ARISTOTLE: 0.8%/yr ENGAGE: 0.85%/yr

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
<b>GI Bleed</b>	0.76%/yr	110 mg: 1.1%/yr 150 mg: 1.5%/yr	1.51%/yr	3.2% (over 1.86 yrs on drug)	RE-LY: 1%/yr ROCKET-AF: 2.2% ARISTOTLE: 0.86%/yr ENGAGE: 1.23%/yr
<b>Drug Interactions</b>  <i>* Note: This is NOT a complete list, rather examples of the more frequent or serious drug interactions with these OACs.</i>	CYP3A4 and P-glycoprotein (e.g., anticonvulsants, rifampin, dexamethasone, trazodone, amiodarone, cyclosporine, diltiazem, verapamil, azole antifungals, macrolides, efavirenz, ritonavir, St. John's Wort) Other agents that effect bleeding	P-glycoprotein (e.g., carbamazepine, rifampin, dexamethasone, trazodone, amiodarone, dronedarone, quinidine, cyclosporine, diltiazem, verapamil, ketoconazole, St. John's Wort) Acid neutralizers Other agents that effect bleeding	Concomitant strong inhibitors/inducer of P-gp will impact edoxaban exposure. Anticonvulsants, rifampin, amiodarone, dronedarone, azole antifungals, macrolides, quinidine, verapamil, St. John's Wort, other agents that effect bleeding	CYP3A4 and P-glycoprotein (e.g., anticonvulsants, rifampin, dexamethasone, trazodone, amiodarone, cyclosporine, diltiazem, verapamil, azole antifungals, macrolides, efavirenz, ritonavir, St. John's Wort) Other agents that effect bleeding	CYP2C9 and CYP3A4 (e.g., anticonvulsants, rifampin, amiodarone, azole antifungals, macrolides, efavirenz, St. John's Wort), vitamin K containing foods, other agents that effect bleeding
<b>Comments</b>		Prodrug – dabigatran exetilate (needs acidic environment for optimal absorption)			
<b>Time to Peak Effect</b>	1-3 hours	1-3 hours	1-2 h	3-4 hours	3-5 days
<b>Half-life</b>	8-15 hours	14-17 hours	10-14h	7-11 hours	20-60 hours
<b>Bioavailability</b>	66%	6%	62%	>80%	Rapid and extensive
<b>Renal Excretion of unchanged Active Drug</b>	27% renal	80% renal	50%	36% renal	Minimal
<b>Effect of Food</b>	No reported effect	Delayed absorption	Food increases peak exposure to varying degrees, but has minimal effect on total exposure – take with or without food	Increases absorption of 20 mg dose but not 10 mg dose (take with food)	Slows rate but not extent; Vitamin K content should be kept consistent
<b>Usual Dosing in Atrial Fibrillation</b>	5mg BID 2.5mg BID if ≥2 of: age≥80, wt≤60kg,	150mg BID 110mg BID	60 mg once daily 30 mg once daily if any one of the following:	20mg OD 15mg OD (if CrCl 30-49)	Initial: 2.5-10 mg daily Maintenance based on INR (target 2.5, range 2-3)

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
	SrCr≥133		weight ≤ 60kg; or if CrCl between 30-50 mL/min		
<b>Consideration in Renal Dysfunction</b>	<p>Determine estimated creatinine clearance in all patients before initiating using Cockcroft-Gault formula.</p> <p>For prevention of stroke and systemic embolism in patients according to renal function. Reduction in dose to 2.5 mg bid, if 2 or more of the following criteria are met:</p> <ul style="list-style-type: none"> <li>- Age &gt; 80 years</li> <li>- Body weight &lt; 60 kg</li> <li>- Serum creatinine &gt; 133 μmol/L</li> </ul> <p>In patients with CrCl &gt;25 mL/min In patients &gt;15, &lt;24 mL/min – no dosing recommendation due to very limited clinical data &lt;15mL/min or undergoing dialysis – not recommended</p>	<p>Determine estimated creatinine clearance in all patients before initiating using Cockcroft-Gault formula.</p> <p>For prevention of stroke and systemic embolism in patients according to renal function: No dose adjustment is generally needed in patients with moderate renal impairment (CrCl 30-50mL/min)</p>	<p>Determine estimated creatinine clearance in all patients before initiating using Cockcroft-Gault formula. CrCl 30-50 mL/min 30 mg daily CrCl &lt; 30mL/min – not recommended</p>	<p>Determine estimated creatinine clearance in all patients before initiating using Cockcroft-Gault formula. Indicated in patients with CrCl as low as 15 mL/min: For prevention of stroke and systemic embolism in patients with atrial fibrillation decrease dose to 15mg daily in patients with moderate to severe renal dysfunction (49-15 mL/min) Not indicated in those patients with CrCl &lt;15 mL/min</p>	
<b>Anticoagulation Monitoring</b>	Not Required	Not Required	Not required	Not Required	Regular INR testing
<b>Additional Monitoring</b>	SCr at baseline and at least annually	SCr at baseline and at least annually	SCr at baseline and at least annually	SCr at baseline and at least annually	
<b>Antidote /Reversal</b>	<p>Antidote*: not yet available in Canada; studies with Andexanet ongoing.</p> <p>Octaplex/Beriplex</p>	<p>Antidote*: Praxbind® (idarucizumab)</p> <p>Some suggestion that activated charcoal if ≤2hr or dialysis (though not</p>	<p>Antidote*: not yet available in Canada; studies with Andexanet</p> <p>Octaplex/Beriplex (Prothrombin Complex) -</p>	<p>Antidote*: not yet available in Canada; studies with Andexanet</p> <p>Octaplex/Beriplex (Prothrombin Complex) -</p>	Vitamin K and Prothrombin Complex Concentrate: ( <i>Chest</i> 2012;141:e152S-e184S)

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
<b>*The shorter half-lives of the four DOACs and their impact on only one aspect of the clotting cascade relative to warfarin will allow for more rapid elimination in the context of normal renal function</b>	<p>(Prothrombin Complex) - may be considered for use in major bleeding (Off-label use and supplied by Canadian Blood Services)</p> <p>Prothrombin complex concentrate may provide benefit though not supported by clinical trials</p> <p>Some suggestion that activated charcoal if <math>\leq 2</math>hr (potentially out to 6 hours) based on one small trial.</p>	<p>likely feasible if patient hypotensive and/or experiencing marked blood loss) may provide benefit though not supported by clinical trials</p> <p>Administer 2 - 2.5 g doses by IV infusion (5-10 mins for each vial) within 15 minutes of each other or as consecutive IV boluses</p>	<p>may be considered for use in major bleeding (Off-label use and supplied by Canadian Blood Services)</p> <p>Some suggestion that activated charcoal if <math>\leq 3</math>hr or prothrombin complex concentrate may provide benefit though not supported by clinical trials</p>	<p>may be considered for use in major bleeding (Off-label use and supplied by Canadian Blood Services)</p> <p>Prothrombin complex concentrate may provide benefit though not supported by clinical trials</p> <p>- Prothrombin Complex Concentrate has very preliminary evidence in 12 healthy volunteers (Circulation 2011;124:1573–1579 [limited study])</p> <p>Some suggestion that activated charcoal if <math>\leq 2</math>hr (potentially out to 8 hours) based on one small trial.</p>	
<b>Hold for Invasive Surgery</b>	<p>At least 24 hours</p> <p>Resumed postoperatively when homeostasis ensured</p>	<p>1-2 days (if CrCl<math>\geq 50</math>) 3-5 days (if CrCl<math>&lt; 50</math>)</p> <p>Hold for 24 hours prior to ablation for atrial fibrillation</p> <p>Resumed postoperatively when homeostasis ensured</p>	<p>At least 24 hours</p> <p>Resumed postoperatively when homeostasis ensured</p>	<p>At least 24 hours</p> <p>Resumed postoperatively when homeostasis ensured</p>	<p>5 days</p> <p>Resumed postoperatively when homeostasis ensured</p>
<b>\$ per month/coverage in Canada</b>	<p>Special authorization for AFib in public drug plans \$3.20/day</p>	<p>Special authorization for AFib in public drug plans \$3.20/day</p>	<p>Special authorization for AFib in public drug plans \$2.84/day</p>	<p>Special authorization for AFib in public drug plans \$2.84/day</p>	<p>Full benefit \$0.06/day, \$1.16/day including monitoring costs</p>
<b>Switching from warfarin to DOAC</b>	<p>Start after warfarin discontinued and INR<math>&lt; 2.0</math></p>	<p>Start after warfarin is discontinued and INR<math>&lt; 2.0</math></p>	<p>Start after warfarin discontinued and INR<math>\leq 2.5</math></p>	<p>Start after warfarin discontinued and INR<math>\leq 2.5</math></p>	
<b>Switching from DOAC to warfarin</b>	<p>Initiate warfarin and continue apixaban until INR<math>\geq 2.0</math></p>	<p>CrCl<math>&gt; 50</math>ml/min: start warfarin 3 days before discontinuing dabigatran</p>	<p>Give edoxaban 30 mg daily (15 mg daily of those on a reduced dose) concurrently with</p>	<p>CrCl<math>&gt; 50</math>ml/min: start warfarin 4 days before planning to discontinue rivaroxaban</p>	



	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
	<p>Note that PT/INR is impacted by apixaban</p> <p>During concomitant therapy, initiate INR testing on day 3 and just before apixaban dose</p>	<p>CrCl 31-50ml/min: start warfarin 2 days before discontinuing dabigatran</p> <p>CrCl 15-30ml/min: start warfarin 1 day before discontinuing dabigatran</p> <p>Note that PT/INR may be impacted by dabigatran</p>	<p>warfarin until INR is <math>\geq 2.0</math> then stop edoxaban</p>	<p>CrCl 31-50mL/min: start warfarin 3 days before planning to discontinue rivaroxaban</p> <p>CrCl 15-30mL/min: start warfarin 2 days before planning to discontinue rivaroxaban</p> <p>Continue rivaroxaban with warfarin until INR<math>\geq 2.0</math>. Use usual warfarin start dose for first 2 days of therapy.</p> <p>Note that PT/INR is impacted by rivaroxaban</p> <p>During concomitant therapy, perform INR testing just before rivaroxaban dose (and at least 24 hours after previous rivaroxaban dose)</p>	

Note: \* The MDRD equation has not been validated to guide the adjustment of drug doses in renal impairment so use of the Cockcroft-Gault equation is still recommended. While it is likely that in many cases when the eGFR is 60 mL/min or less that the calculated creatinine clearance will be very similar to the eGFR, differences could occur if the person has a body surface area significantly lower or higher than 1.73 m<sup>2</sup>, or at different stages of renal disease. Drug dose adjustment is based on the actual GFR and the best way of calculating this remains the Cockcroft-Gault equation. The FDA standard for drug dosing recommendations is the Cockcroft-Gault equation. (Sources for Additional Information: <http://www.bpac.org.nz/magazine/2007/june/renal.asp?page=3>; Moranville and Jennings, Am J Health-Syst Pharm. 2009; 66:154-61)