CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

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Appendix Four: Oral Anticoagulants for the Prevention of Stroke in Atrial Fibrillation Patients

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Appendix Four: Oral Anticoagulants for the Prevention of Stroke in Atrial Fibrillation Patients

This table provides a summary of the pharmacotherapeutic properties, side effects, drug interactions and other important information on the five anticoagulant medications currently in use in Canada for the prevention of stroke and systemic embolism in atrial fibrillation. This table should be used as a reference guide by health care professionals when selecting an appropriate agent for individual patients. Patient compliance, side effects, drug interactions and bleeding risk status should all be taken into consideration during decision-making, in addition to other information provided in this table and available elsewhere regarding these medications.

	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

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
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 with other anticoagulants	Active bleeding or significant risk factors for bleeding **CrCl<30 ml/min** 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
Side Effects	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)
Landmark Trials	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
Inclusion Criteria	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-valvularAFib, with history of stroke, TIA, or systemic embolism or at least 2 of the following: Heart failure HTN Age >75 DM	

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Exclusion Criteria	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 ASA >100 mg/d	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; acute coronary syndromes, coronary revascularization or stroke within 30 days prior to randomization; and an inability to adhere to study procedures.	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 Significant liver disease Use of strong CYP 3A4 inhibitors Chronic NSAIDs Pregnancy HIV CrCl<15ml/min ASA >100mg/d	
Primary Outcome Measures: Stroke and Systemic Embolism Event Rate	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
Overall Bleeding	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

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Major Bleeding	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
ICH	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
GI Bleed	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
Drug Interactions **** Note: This is NOT a complete list, rather examples of some of the more frequent or serious drug interactions with these OACs.***	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
Comments		Prodrug – dabigatran exetilate (needs acidic environment for optimal absorption)			
Time to Peak Effect	1-3 hours	1-3 hours	1-2 h	3-4 hours	3-5 days
Half-life	8-15 hours	14-17 hours	10-14h	7-11 hours	20-60 hours
Bioavailability	66%	6%	62%	>80%	Rapid and extensive

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Renal Excretion of unchanged Active Drug	27% renal	80% renal	50%	36% renal	Minimal
Effect of Food	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
Usual Dosing in Atrial Fibrillation	5mg BID 2.5mg BID if ≥2 of: age≥80, wt≤60kg, SrCr≥133	150mg BID 110mg BID	60 mg once daily 30 mg once daily if any one of the following: weight ≤ 60kg; or if CrCl between 30-50 mL/min	20mg OD 15mg OD (if CrCl 30-49)	Initial: 2.5-10 mg daily Maintenance based on INR (target 2.5, range 2-3)
Consideration in Renal Dysfunction	Determine estimated creatinine clearance in all patients before initiating using Cockroft-Gualt formula. 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: - Age > 80 years - Body weight < 60 kg - Serum creatinine > 133 mcmol/L In patients with CrCl >25 ml/min In patients >15, <24 mL/min – no dosing recommendation due to very limited clinical data <15mL/min or undergoing dialyisis – not recommended	Determine estimated creatinine clearance in all patients before initiating using Cockroft-Gualt formula. 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)	Determine estimated creatinine clearance in all patients before initiating using Cockroft-Gualt formula. CrCl 30-50 mL/min 30 mg daily CrCl < 30mL/min – not recommended	Determine estimated creatinine clearance in all patients before initiating using Cockroft-Gualt 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 <15 mL/min	

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Anticoagulation Monitoring	Not Required	Not Required	Not required	Not Required	Regular INR testing
Additional Monitoring	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	
Antidote /Reversal ***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**	Antidote*: not yet available in Canada; studies with Andexanet ongoing. Octaplex/Beriplex (Prothrombin Complex) - may be considered for use in major bleeding (Off-label use and supplied by Canadian Blood Services) Prothrombin complex concentrate may provide benefit though not supported by clinical trials Some suggestion that activated charcoal if ≤2hr (potentially out to 6 hours) based on one small trial.	Antidote*: Praxbind® (idarucizumab) Some suggestion that activated charcoal if ≤2hr or dialysis (though not likely feasible if patient hypotensive and/or experiencing marked blood loss) may provide benefit though not supported by clinical trials 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	Antidote*: not yet available in Canada; studies with Andexanet Octaplex/Beriplex (Prothrombin Complex) - may be considered for use in major bleeding (Off-label use and supplied by Canadian Blood Services) Some suggestion that activated charcoal if ≤3hr or prothrombin complex concentrate may provide benefit though not supported by clinical trials	Antidote*: not yet available in Canada; studies with Andexanet Octaplex/Beriplex (Prothrombin Complex) - may be considered for use in major bleeding (Off-label use and supplied by Canadian Blood Services) Prothrombin complex concentrate may provide benefit though not supported by clinical trials - Prothrombin Complex Concentrate has very preliminary evidence in 12 healthy volunteers (Circulation 2011;124:1573–1579 [limited study]) Some suggestion that activated charcoal if ≤2hr (potentially out to 8 hours) based on one small trial.	Vitamin K and Prothrombin Complex Concentrate: (*Chest* 2012;141;e152S-e184S)
Hold for Invasive Surgery	At least 24 hours Resumed postoperatively when homeostasis ensured	1-2 days (if CrCl≥50) 3-5 days (if CrCl<50) Hold for 24 hours prior to ablation for atrial fibrillation Resumed postoperatively when homeostasis ensured	At least 24 hours Resumed postoperatively when homeostasis ensured	At least 24 hours Resumed postoperatively when homeostasis ensured	5 days Resumed postoperatively when homeostasis ensured

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
$ per month/coverage in Canada	Special authorization for AFib in public drug plans $3.20/day	Special authorization for AFib in public drug plans $3.20/day	Special authorization for AFib in public drug plans $2.84/day	Special authorization for AFib in public drug plans $2.84/day	Full benefit $0.06/day, $1.16/day including monitoring costs
Switching from warfarin to DOAC	Start after warfarin discontinued and INR<2.0	Start after warfarin is discontinued and INR<2.0	Start after warfarin discontinued and INR≤2.5	Start after warfarin discontinued and INR≤2.5	
Switching from DOAC to warfarin	Initiate warfarin and continue apixaban until INR≥2.0 Note that PT/INR is impacted by apixaban During concomitant therapy, initiate INR testing on day 3 and just before apixaban dose	CrCl>50ml/min: start warfarin 3 days before discontinuing dabigatran CrCl 31-50ml/min: start warfarin 2 days before discontinuing dabigatran CrCl 15-30ml/min: start warfarin 1 day before discontinuing dabigatran Note that PT/INR may be impacted by dabigatran	Give edoxaban 30 mg daily (15 mg daily of those on a reduced dose) concurrently with warfarin until INR is ≥2.0 then stop edoxaban	CrCl>50ml/min: start warfarin 4 days before planning to discontinue rivaroxaban CrCl 31-50mL/min: start warfarin 3 days before planning to discontinue rivaroxaban CrCl 15-30mL/min: start warfarin 2 days before planning to discontinue rivaroxaban Continue rivaroxaban with warfarin until INR≥2.0. Use usual warfarin start dose for first 2 days of therapy. Note that PT/INR is impacted by rivaroxaban During concomitant therapy, perform INR testing just before rivaroxaban dose (and at least 24 hours after previous rivaroxaban dose)	

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^2, 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 Cockroft-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)