

Which Direct Oral Anticoagulant (DOAC) Is Best For My Patient?

There are currently four direct oral anticoagulants (DOACs) available in Canada which can be used as alternatives to warfarin.¹ While apixaban (Eliquis®), rivaroxaban (Xarelto®), and edoxaban (Lixiana®) are all direct Factor Xa inhibitors, dabigatran (Pradaxa®) is the only direct thrombin inhibitor currently available.^{1,2} The DOACs are often lumped together and compared to warfarin. The purpose of this newsletter is to provide a comparison among the DOACs themselves. Table 1 is a summary of the information in the newsletter and a guide to determining the best anticoagulant choice for individual patients.

Table 1: Comparison of oral anticoagulants

Patient Situation	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
VTE prophylaxis in surgical patients	✓	✓	⊘	✓	✓
Preference for once daily dosing	⊘	? (only VTE prophylaxis)	✓	? (except first 3 wk of VTE tx)	✓
Desire for therapeutic lab monitoring	⊘	⊘	⊘	⊘	✓
CrCl < 25-30 ml/min	⊘	⊘	⊘	⊘	✓
Extremes in weight	⚠	⚠	⚠	⚠	✓
Patient places high value on antidote availability [†]	⚠	✓	⚠	⚠	✓
Takes a drug that strongly inhibits both CYP3A4 and P-gp*	⊘	⊘	⊘	⊘	⚠
Takes a drug that strongly inhibits P-gp only	⚠	⊘	⊘	⚠	✓
Takes a drug that strongly inhibits CYP3A4 only*	⚠	✓	✓	⚠	⚠
Takes a drug that induces both CYP3A4 and P-gp*	⊘	⊘	⊘	⊘	⚠
Takes a drug that induces P-gp only	⊘	⊘	⊘	⊘	✓
Takes a drug that induces CYP3A4 only*	⊘	✓	✓	⊘	⚠
Takes a drug that inhibits or induces CYP1A2, CYP2C9 or CYP2C19*	✓	✓	✓	✓	⚠
Relies on SDEBB (? = EDS required)	?	?	⊘	?	✓
Relies on NIHB (? = PA required)	?	?	⊘	?	✓

[†]Patients should be counseled that antidote for dabigatran will only be available at larger centres and reserved for severe cases.³ Supportive care (as opposed to antidote administration) is recommended treatment in most cases and is most likely what patient will receive regardless of antidote availability.

*Warfarin interacts with these drugs but can be managed with INR monitoring; however, this can be cumbersome if the interacting drug is for short term use (e.g. antibiotic)

✓ Preferred agent/no restrictions ⚠ Caution/monitor/weigh benefit vs risk /other agent(s) preferred ⊘ Avoid ? If criteria met

CrCl = creatinine clearance; NIHB = non-insured health benefits; P-gp = P-glycoprotein; SDEBB= Saskatchewan Drug & Extended Benefits Branch; tx = treatment; VTE=venous thromboembolism; wk= week(s)

Do DOACs have different indications?

The DOACs are indicated for all the conditions listed in Table 2 with the exception of edoxaban for VTE prophylaxis in surgical patients.

Table 2: Indications for DOACs ^{1,2,4}

Indication	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
VTE Prophylaxis in Surgical Patients	✓	✓	Not indicated	✓
VTE Treatment	✓	✓	✓	✓
Prevention of Recurrent VTE	✓	✓	✓	✓
AF (non-valvular*) Stroke Prevention	✓	✓	✓	✓
Valvular* AF	Not indicated	Contraindicated*	Not indicated	Not indicated

*Based on RE-ALIGN,⁵ which was stopped early due to increased rates of thromboembolic and bleeding complications and no clear benefit. AF=atrial fibrillation; VTE = venous thromboembolism

Note: Valvular atrial fibrillation implies rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

Is one DOAC more convenient to take than another?

Administration²:

Edoxaban and apixaban can be administered without regard to meals. Dabigatran can also be administered without regard to meals; however, if dyspepsia occurs it is advised to administer with meals. Rivaroxaban is to be taken with meals in doses > 10 mg.

Dosing Frequency^{1,2}:

Apixaban requires twice daily dosing for all indications. Dabigatran is twice daily for all indications with the exception of VTE prophylaxis in which it is administered once daily. Edoxaban is once daily for all indications. Rivaroxaban is once daily for all indications with the exception of VTE treatment, in which it is twice daily for the first three weeks of treatment then once daily thereafter. Actual doses vary by indication; consult product monographs for more information.

Monitoring^{2,6}:

INR monitoring is not appropriate for DOACs. Dabigatran may be monitored through the activated partial thromboplastin time but this is not regularly done and often not reliable. Because all DOACs are affected by impaired renal function, creatinine clearance (CrCl) should be determined every 6 to 12 months.¹ Adherence and signs of bleeding should also be assessed at each refill.

Does the risk of important adverse effects differ among DOACs?

Table 3 summarizes the differences in risk of important adverse effects among DOACs.

Table 3: DOACs and important adverse effects

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Bleeding-Related Readmission Rate: apixaban vs. others⁷	-	1.2 to 1.3-fold greater	-	1.4 to 1.6-fold greater
All-Cause Hospital Mortality: apixaban vs. others⁷	-	-	-	1.2-fold greater
Major Bleeding⁸	No difference vs. dabigatran	No difference vs. rivaroxaban	-	Higher vs. apixaban (HR: 1.82; 95 % CI: 1.36-2.43)

CI= confidence interval; HR = hazard ratio

What are the contraindications and drug interactions of DOACs?

While drug interactions of DOACs are fewer than those of warfarin, they are not well-characterized at this point. Pharmacodynamic interactions with other drugs that may increase the risk of bleeding are important considerations. Pharmacokinetic interactions usually involve inhibition or induction of cytochrome P450 3A4 (CYP3A4) and/or P-glycoprotein (P-gp). Substrates, inhibitors, and Inducers--especially those of P-gp--are still being uncovered and confirmed by research. Unlike

warfarin, laboratory monitoring is not available to monitor the effects of potentially interacting drugs on DOAC activity. Table 4 lists inhibitors and inducers of CYP3A4 and P-gp. *Italic* font indicates drugs that are not well-established as a noted inducer or inhibitor. There are some discrepancies in terms of relative inhibitory potencies of some drugs and not all references will agree with the chosen classification. Care has been taken to create the most comprehensive yet useful table; however, it should be noted some of the interactions are theoretical and undoubtedly some drugs with potential to cause an interaction will not have been included because they have not yet been recognized as an inhibitor or inducer. Always check current references for potential interactions.

Table 4: DOAC contraindications and drug interactions* 1,2,9-12

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Contraindications				
All DOACs according to Canadian labelling	<u>Absolute:</u> Active bleeding or risk of clinically significant bleed, hypersensitivity, concurrent use of other oral anticoagulants (not including bridging to warfarin)			
	<u>Relative:</u> Extremes in body weight, fall history, hemorrhagic disorders; renal impairment [‡]			
DOAC-specific according to Canadian labelling	- Coagulation – associated hepatic disease (CAHD) - strong INH of both CYP3A4 & P-gp	- CrCl <30 ml/min - lactation - prosthetic heart valves - strong INH of P-gp	- CAHD - lactation - pregnancy	- CAHD - lactation - pregnancy - strong INH of both CYP3A4 & P-gp
Drug Interactions				
All DOACs	- antiplatelets, NSAIDs, SSRIs (pharmacodynamic); IND of P-gp			
DOAC-Specific	- antacids (space by ≥ 2h); - IND of CYP3A4 &/or P-gp - strong INH CYP3A4 <u>or</u> P-gp only	- moderate INH P-gp - adjust dose [†] if on: amiodarone, quinidine or verapamil	- moderate to strong INH P-gp	- IND of CYP3A4 &/or P-gp - strong INH CYP3A4 <u>or</u> P-gp only
Strong INH CYP3A4 and P-gp : clarithromycin, itraconazole, ketoconazole, posaconazole, ritonavir; <i>verapamil</i> .				
Strong INH CYP3A4: clarithromycin, dronedarone, HIV PIs, itraconazole, ketoconazole, posaconazole, ritonavir				
Moderate INH CYP3A4: amiodarone, diltiazem, erythromycin, fluconazole, grapefruit, verapamil; <i>fluvoxamine, imatinib, mifepristone, nefazodone</i>				
Strong INH P-gp: clarithromycin, cyclosporine, itraconazole, ketoconazole, posaconazole, ritonavir				
Moderate INH P-gp: amiodarone, carvedilol, conivaptan, diltiazem, dronedarone, erythromycin, HIV PIs, quinidine, verapamil, voriconazole; <i>azithromycin, cobicistat, duloxetine, grapefruit, mefloquine, mifepristone, propafenone, tacrolimus, tamoxifen, telithromycin, ticagrelor</i> .				
IND CYP3A4: carbamazepine, phenytoin, phenobarbital, rifampin; <i>bosentan, efavirenz, rifabutin St. John's Wort</i>				
IND P-gp: carbamazepine, rifampin, St. John's Wort, tipranavir				
HIV PIs (other than ritonavir): atazanavir, darunavir, indinavir, fosamprenavir, lopinavir, nelfinavir, tipranavir				
*Information presented is not intended to be a complete list of all drug interactions and/or contraindications				
‡While impaired renal function is an official contraindication for only dabigatran, none of the agents are recommended in severe renal impairment; rivaroxaban and edoxaban should be avoided in patients with CrCl < 30 ml/min ² ; and apixaban in those with CrCl <25 ml/min. ^{2,13}				
†Depends on indication; see product monograph for details.				
CAHD = coagulation-associated hepatic disease; CrCl= creatinine clearance; CYP3A4 = Cytochrome P450 3A4; DOAC = direct oral anticoagulant; HIV= human immunodeficiency virus; IND= inducer; INH = inhibitor; NSAID= non-steroidal anti-inflammatory drug; P-gp= P-glycoprotein; PI= protease inhibitor; PPI = proton pump inhibitor; SSRI= selective serotonin reuptake inhibitor				

Is there an antidote for the DOACs? 1,6,14,15

Praxbind® (idarucizumab), an antidote for dabigatran, has recently become available. As the name suggests, Praxbind® inhibits dabigatran by directly binding to it. Each dose of Praxbind is approximately \$4500 CAD,¹⁶ so its use will be limited to patients with severe bleeding.

Currently no antidote is available for the direct factor Xa inhibitors, although a phase III study of a possible antidote, andexanet alfa, is currently underway.¹⁷ Andexanet has been described as a decoy because it acts like factor Xa; the factor Xa inhibitors bind with greater affinity to andexanet than to factor Xa thereby reducing the inhibition of factor Xa activation. Severe bleeding may be managed with four-factor prothrombin complex concentrates (PCCs) for the factor Xa inhibitors or activated PCC for all DOACs.

Costs/coverage of the DOACs?

The cost of the different DOACs is very similar but their Formulary status differs as summarized in Table 5

Table 5: Saskatchewan Drug Formulary Status and Cost of DOACs

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Approximate Monthly Cost*¹ (typical dosing for most indications)	\$116	\$119	\$109	\$105
Formulary Status (as of 01 Jul 2017)	SDEBB ¹⁸ NIHB ¹⁹	EDS PA	EDS PA	Not a benefit PA
EDS=exceptional drug status; NIHB=Non-Insured Health Benefits; PA= prior approval; SDEBB=Saskatchewan Drug Plan & Extended Benefits Branch				
*Monthly cost for warfarin ≤ 5 mg daily ~ \$15 ¹ (does not include cost to the patient/ healthcare system of INR testing, travel, etc.)				

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