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Drug interactions with non-vitamin K antagonist oral anticoagulants (NOACs): Handle with care

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Dabigatran and rivaroxaban were the first non-vitamin K antagonist oral anticoagulants (NOACs) on the market in Canada in 2008, followed by apixaban in 2012.¹⁻³ By 2013 they accounted for 23.5% of all prescriptions for oral anticoagulants in Canada.⁴ Compared to warfarin, NOACs have rapid onset of action, no routine coagulation monitoring and fewer drug interactions.⁵⁻⁸ Yet, case reports of treatment failure and life-threatening bleeding suggest NOACs have problematic drug interactions.⁹⁻²¹

Drugs interact with NOACs by pharmacodynamic and/or pharmacokinetic mechanisms. Inhibition or induction of transporter proteins and metabolizing enzymes cause bleeding (from elevated drug levels) and thromboembolism (from decreased drug levels).²²⁻²⁴ Permeability-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) are transporter proteins in the intestinal cell, liver and kidney that excrete drugs into the intestinal lumen, bile duct and urine.²⁵ Both transport apixaban and rivaroxaban.^{5,8} The prodrug, dabigatran etexilate - not its active metabolite, dabigatran - is transported by P-gp.^{7,26} See table 1 in this article for more information.

Information on drug interactions with NOACs is incomplete.²⁷ Evidence guiding the safety of drugs used with NOACs includes subanalyses of randomized controlled trials, adverse drug reaction databases, pharmacokinetic studies and spontaneous case reports, but careful

interpretation is required.^{28,29}

For example, pharmacokinetic studies in healthy volunteers found that strong inhibitors of both CYP3A4 and P-gp/BCRP (e.g. ketoconazole) lead to clinically important elevation of rivaroxaban drug concentrations, whereas moderate inhibitors of CYP3A4 and/or P-gp (e.g. erythromycin) did not.³⁰ However, rivaroxaban is 66% eliminated by the kidneys. Subsequent studies in subjects with mild and moderate renal impairment found clinically important elevation of rivaroxaban concentrations when administered with erythromycin.³¹ Care should be given when prescribing NOACs that are primarily eliminated by the kidneys (i.e. dabigatran and rivaroxaban) to those with abnormal renal function.

Though the pharmacokinetic effects of combining two or more mild/moderate CYP3A4 and P-gp inhibitors with NOACs has not been studied, limited evidence from a subanalysis of the ROCKET AF trial reported increased bleeding rates among patients treated with rivaroxaban plus two or more of these agents.³² Combining NOACs with two or more drugs that have a cautionary interaction status may require adjustment of therapy.²⁷ See table 2 for risk factors for bleeding with oral anticoagulants.

For unstudied drug combinations, knowledge of the potency of the drug's inhibition/induction of P-gp, BCRP and CYP3A4 may predict drug interactions with NOACs, though this information may not be available for older drugs. One guideline conservatively recommends avoiding drug combinations that lack pharmacokinetic or safety studies.²⁷

Pharmacists can optimize safe use of NOACs by:

- Ensuring correct dose for indication, age and renal function.
- Obtaining a thorough drug history.
- Reducing polypharmacy, risks for bleeding and drug interactions.
- Recommending yearly renal function tests.
- Questioning patients about side effects and adherence.

Suspected drug interactions causing adverse drug reactions should be reported to Health Canada, along with a full list of the concomitant medications. Such reports were recently used by Health Canada - in conjunction with other databases, published cases and studies - to review and update the safety information regarding combining dabigatran with either dronedarone or amiodarone.³³ Remember to submit a report as it may have an impact on safe use of NOACs in the future.

Recommended online resources:

- Health Canada Drug Product Database (most current product monograph).
- BC Guidelines article: Use of NOACs in non-valvular atrial fibrillation.
- Updated European Heart Rhythm Association Practical Guide on the use of NOACs in patient with non-valvular atrial fibrillation (Oxford University Press).²⁷

Table 1: Pharmacokinetic profile and general drug interaction guide[†] for NOACs

	apixaban (Eliquis) ^{5,34}	dabigatran etexilate (Pradax) ⁷	rivaroxaban (Xarelto)
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Distribution	P-gp and BCRP	P-gp (dabigatran etexilate but not dabigatran)	P-gp and BCRP
Metabolism	CYP3A4/5 (major) CYP1A2, 2C8, 2C9, 2C19, 2J2 (minor)	Esterases	CYP3A4/5 (18%), CYP1A2 (12%), CYP2C9 (12%), CYP2C19 (12%), CYP2J2 (12%) hydrolysis (14%)
Elimination	27% in urine	85% in urine	66% in urine (parent and metabolites) 33% in feces (metabolites)
Combinations contraindicated	<i>Strong</i> inhibitors/inducers of <u>both</u> CYP3A4/5 and P-gp	<i>Strong/moderate</i> inhibitors/inducers of P-gp	<i>Strong</i> inhibitors/inducers of CYP3A4/5 and P-gp
Combinations with caution	<i>weak/moderate</i> inhibitors/inducers of CYP3A4/5 <u>or</u> P-gp or BCRP	<i>weak</i> inhibitors/inducers P-gp Administer dabigatran etexilate 2 hours prior	<i>weak/moderate</i> inhibitors/inducers of CYP3A4/5 <u>or</u> P-gp
	Two or more drugs reassess need à deprescribe or adjust dose ²⁷		
Additional considerations	Adjust dose for age and renal function	Adjust dose for age, renal function and coadministration of P-gp inhibitors	Adjust dose for age, renal function and coadministration of P-gp inhibitors

†Intended as a guide only, consult other resources

Table 2: Risk factors for bleeding with oral anticoagulants^{5,7,8,27,35,36}

Pharmacodynamic interactions	Disease states	Other
May increase risk of bleeding by 50-100%		

Corticosteroids, systemic	Coagulation disorders/low platelets	Age > 75
Natural health care products (e.g. ginkgo biloba, garlic, Asian ginseng and danshen).	Gastrointestinal or intracranial bleed, recent	Polypharmacy
NSAIDs	Gastrointestinal ulcerative disease, active	Weight > 90 kg
Platelet aggregation inhibitors	Hypertension, uncontrolled severe	
SSRIs, SNRIs	Pulmonary bleeding, history	
	Recent surgery, biopsy or trauma	
	Renal function decline	

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