INESSS
LE SAVOIR PREND FORME

DRUG INTERACTIONS WITH DIRECT ORAL ANTICOAGULANTS

For further details, click on the underlined words.

This tool is a nonexhaustive list of potential or confirmed drug interactions with direct oral anticoagulants (DOACs) intended for health professionals. It is provided for information purposes only and should not replace the judgement of the clinician who performs reserved activities by an act or a regulation. This list was prepared using a systematic process. It is supported by the data available, when this tool was published, in product monographs and the scientific literature, and by the knowledge and experience of Québec clinicians and experts. For further details, go to inesss.qc.ca.

OVERVIEW OF INTERACTIONS

	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
1 SYSTEMIC ANTI-INFECTIVES				
Antibacterials (macrolides and rifamycins)	Interaction with certain drugs in this class. Consult the detailed table.			
Azole antifungals				
Direct-acting antivirals (HIV protease inhibitors)	✕	Interaction with certain drugs in this class. Consult the detailed table.	✕	⚠
2 ANTINEOPLASTICS AND IMMUNOMODULATORS				
Immunosuppressants (cyclosporine and tacrolimus)	⚠	Interaction with certain drugs in this class. Consult the detailed table.	⚠	⚠
3 ANTITHROMBOTICS				
Antiplatelet agents	Interaction with certain drugs in this class. Consult the detailed table.			
Heparins	✕	✕	✕	✕
Direct thrombin inhibitors	✕	✕	✕	✕
Other (fondaparinux)	✕	✕	✕	✕
4 DIGESTIVE TRACT				
Antacids	✓	✓	✓	Interaction with certain drugs in this class. Consult the detailed table.
H_2-receptor antagonists	✓	✓	✓	⚠
Proton pump inhibitors	✓	✓	✓	⚠

✓ No interaction or interaction considered clinically nonsignificant (no dosage change necessary).

⚠ Can be administered concomitantly with caution.

✕ Completely avoid concomitant administration.

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OVERVIEW OF INTERACTIONS (CONT'D)

	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
5 CARDIOVASCULAR SYSTEM				
Antiarrythmics (amiodarone, dronedarone, quinidine)	⚠	Interaction with certain drugs in this class. Consult the detailed table.		
Beta-blockers (atenolol and others)	✓	✓	✓	✓
Cardiotonic glycosides (digoxin)	✓	⚠	✓	✓
Lipid-lowering agents (HMG-CoA reductase inhibitors)	✓	✓	✓	✓
Selective calcium channel blockers (diltiazem, verapamil)	⚠	⚠	⚠	Interaction with certain drugs in this class. Consult the detailed table.
6 MUSCULOSKELETAL SYSTEM				
Nonsteroidal antiinflammatory drugs	⚠	⚠	⚠	⚠
7 NERVOUS SYSTEM				
Antidepressants (SSRIs, SNRIs and others)	⚠	⚠	⚠	⚠
Antiepileptics (carbamazepine, phenobarbital, primidone, phenytoin)	✗	✗	✗	✗
8 OTHERS				
Foods and natural products (St. John's wort, grapefruit juice)	Interaction with certain drugs in this class. Consult the detailed table.			

✓ No interaction or interaction considered clinically nonsignificant (no dosage change necessary).

⚠ Can be administered concomitantly with caution.

✗ Completely avoid concomitant administration.

ACRONYMS AND ABBREVIATIONS

AUC: area under the curve
C_{max}: peak concentration
PE: pulmonary embolism
P-gp: P-glycoprotein
LMWH: low-molecular-weight heparin
SNRI: selective serotonin-norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
DVT: deep vein thrombosis
HIV: human immuodeficiency virus

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❶ SYSTEMIC ANTI-INFECTIVES

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Concomitant drug	Mechanism	Apixaban (CYP3A4 and P-gp substrate)	Edoxaban (P-gp substrate)	Rivaroxaban (CYP3A4 and P-gp substrate)	Dabigatran (P-gp substrate)
ANTIBACTERIALS					
Azithromycin	**Pharmacokinetic interaction** P-gp inhibition (moderate)	No data	PE and DVT - If concomitant administration of short duration: **Reduce edoxaban dosage to 30 mg daily**	No data	* **Caution in patients with a CrCl < 50 ml/min.**
Clarithromycin	**Pharmacokinetic interaction** Inhibition of CYP3A4 (strong) and P-gp (moderate)	↑ 60% in AUC ↑ 30% in C_{max}	If concomitant administration of short duration: **Reduce edoxaban dosage to 30 mg daily**	↑ 50% in AUC ↑ 40% in C_{max}	* ↑ 19% in AUC ↑ 15% in C_{max} * **Caution in patients with a CrCl < 50 ml/min.**
Erythromycin	**Pharmacokinetic interaction** Inhibition of CYP3A4 and P-gp (moderate)	No data	↑ 85% in AUC ↑ 68% in C_{max} **Reduce edoxaban dosage to 30 mg daily**	↑ 30% in AUC and in C_{max} **No dosage change necessary**	No data
Rifampicin/ rifampin	**Pharmacokinetic interaction** Strong induction of CYP3A4 and P-gp	↓ 54% in AUC ↓ 42% in C_{max}	↓ 34% in AUC No effect on C_{max}	↓ 50% in AUC	↓ 67% in $AUC_{0\text{-}inf}$ ↓ 66% in C_{max}
AZOLE ANTIFUNGALS					
Fluconazole	**Pharmacokinetic interaction** CYP3A4 inhibition (moderate)	No data	No data	↑ 40% in AUC ↑ 30% in C_{max}	No data
Itraconazole	**Pharmacokinetic interaction** Inhibition of CYP3A4 and P-gp (strong)		If concomitant administration of short duration: **Reduce edoxaban dosage to 30 mg daily**	↑ 160%	Can increase exposure
Ketoconazole	**Pharmacokinetic interaction** Inhibition of CYP3A4 and P-gp (strong)	↑ 100% in AUC ↑ 60% in C_{max}	↑ 87% in AUC ↑ 89% in C_{max} **Reduce edoxaban dosage to 30 mg daily**	↑ 160% in AUC ↑ 70% in C_{max}	↑ 138-153% in AUC ↑ 135-149% in C_{max}
Posaconazole	**Pharmacokinetic interaction** Inhibition of CYP3A4 and P-gp		No data	↑ 160%	Can increase exposure
Voriconazole	**Pharmacokinetic interaction** CYP3A4 inhibition (strong)		No data		No data
DIRECT-ACTING ANTIVIRALS (HIV PROTEASE INHIBITORS)					
Ritonavir	**Pharmacokinetic interaction** Strong inhibition of CYP3A4 and P-gp		* Potential ↑ of 50-100% in exposure * **If considered necessary, use with caution**	↑ 150% in AUC ↑ 60% in C_{max}	Can increase exposure
Others	**Pharmacokinetic interaction** Inhibition of CYP3A4 and P-gp		* Potential ↑ of 50-100% in exposure * **If considered necessary, use with caution**		Can increase exposure

❷ ANTINEOPLASTICS AND IMMUNOMODULATORS

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Concomitant drug	Mechanism	Apixaban (CYP3A4 and P-gp substrate)	Edoxaban (P-gp substrate)	Rivaroxaban (CYP3A4 and P-gp substrate)	Dabigatran (P-gp substrate)
IMMUNOSUPPRESSANTS					
Cyclosporine	**Pharmacokinetic interaction** Inhibition of CYP3A4 (weak) and P-gp (moderate)	⚠ ↑ 43% in C_{max}	⚠ ↑ 73% in AUC ↑ 74% in C_{max} **Reduce edoxaban dosage to 30 mg daily**	⚠ No data	⚠ Can increase exposure
Tacrolimus	**Pharmacokinetic interaction** CYP3A4 substrate and P-gp inhibition	⚠ ↓ 22% in AUC	⚠ No data	⚠ No data	⚠ Can increase exposure

❸ ANTITHROMBOTICS

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Concomitant drug	Mechanism	Apixaban (CYP3A4 and P-gp substrate)	Edoxaban (P-gp substrate)	Rivaroxaban (CYP3A4 and P-gp substrate)	Dabigatran (P-gp substrate)
ANTIPLATELET AGENTS					
Acetylsalicylic acid	**Pharmacodynamic interaction** ↑ bleeding risk	⚠ No effect on pharmacokinetics	⚠ ↑ 32% in AUC ↑ 35% in C_{max}	⚠ No effect on pharmacokinetics	⚠
Clopidogrel	**Pharmacokinetic and pharmacodynamic interaction** CYP3A4 inhibition and ↑ bleeding risk	⚠ No effect on pharmacokinetics	⚠	⚠ ↑ bleeding time No effect on bioavailability or pharmacokinetics	⚠ ↑ 30-40% in AUC ↑ 30-40% in C_{max}
Prasugrel	**Pharmacodynamic interaction** ↑ bleeding risk	⊗	⊗	⊗	⊗
Ticagrelor	**Pharmacokinetic and pharmacodynamic interaction** Inhibition of P-gp and ↑ bleeding risk	⊗	⊗	⊗	⊗ ↑ 27-49% in AUC ↑ 24-65% in C_{max}
HEPARINS					
Low-molecular-weight heparins (LMWHs)	**Pharmacodynamic interaction** ↑ bleeding risk	⊗	⊗	⊗	⊗
Unfractionated heparin	**Pharmacodynamic interaction** ↑ bleeding risk	⊗ Except at the doses required to ensure central venous or arterial catheter patency	⊗ Except at the doses required to ensure central venous or arterial catheter patency	⊗ Except at the doses required to ensure central venous or arterial catheter patency	⊗ Except at the doses required to ensure central venous or arterial catheter patency
DIRECT THROMBIN INHIBITORS					
Argatroban	**Pharmacodynamic interaction** ↑ bleeding risk	⊗	⊗	⊗	⊗
Bivalirudine	**Pharmacodynamic interaction** ↑ bleeding risk	⊗	⊗	⊗	⊗
OTHERS					
Fondaparinux	**Pharmacodynamic interaction** ↑ bleeding risk	⊗	⊗	⊗	⊗

❹ DIGESTIVE TRACT

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Concomitant drug	Mechanism	Apixaban (CYP3A4 and P-gp substrate)	Edoxaban (P-gp substrate)	Rivaroxaban (CYP3A4 and P-gp substrate)	Dabigatran (P-gp substrate)
ANTACIDS					
Aluminum compounds, sodium bicarbonate, calcium and/or magnesium compounds, or a combination thereof	**Pharmacokinetic interaction** ↑ gastric pH	✓ No data	✓ No data	✓ No effect on bioavailability or pharmacokinetics	⚠ ↓ 11 to 35% **Administer dabigatran at least 2 hours before an antacid**
H_2-RECEPTOR ANTAGONISTS					
Cimetidine	**Pharmacokinetic interaction** ↑ gastric pH	✓ No data	✓ No data	✓ No data	⚠ No data
Famotidine	**Pharmacokinetic interaction** ↑ gastric pH	✓ No effect on pharmacokinetics	✓ No data	✓ No data	⚠ No data
Ranitidine	**Pharmacokinetic interaction** ↑ gastric pH	✓ No data	✓ No data	✓ No effect on bioavailability or pharmacokinetics	⚠ No data
PROTON PUMP INHIBITORS (PPIs)					
Dexlansoprazole	**Pharmacokinetic interaction** ↑ gastric pH	✓ No data	✓ No data	✓ No data	⚠ No data
Esomeprazole	**Pharmacokinetic interaction** ↑ gastric pH	✓ No data	✓ ↓ 33% in C_{max} **No dosage change necessary**	✓	⚠ No data
Lansoprazole	**Pharmacokinetic interaction** ↑ gastric pH	✓ No data	✓ No data	✓ No data	⚠ No data
Omeprazole	**Pharmacokinetic interaction** ↑ gastric pH	✓ No data	✓ No data	✓ No effect on bioavailability or pharmacokinetics	⚠ No data
Pantoprazole	**Pharmacokinetic interaction** ↑ gastric pH	✓ No data	✓ No data	✓ No data	⚠ ↓ 30% in AUC **No dosage change necessary**
Rabeprazole	**Pharmacokinetic interaction** ↑ gastric pH	✓ No data	✓ No data	✓ No data	⚠ No data

5 CARDIOVASCULAR SYSTEM

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Concomitant drug	Mechanism	Apixaban (CYP3A4 and P-gp substrate)	Edoxaban (P-gp substrate)	Rivaroxaban (CYP3A4 and P-gp substrate)	Dabigatran (P-gp substrate)
ANTIARRYTHMICS					
Amiodarone	**Pharmacokinetic interaction** Inhibition of CYP3A4 and P-gp (moderate)	⚠ ↑ 40% in AUC ↑ 30% in C_{max} Data extrapolated from data on diltiazem (according to product monograph)	⚠ ↑ 40% in AUC ↑ 66% in C_{max} **No dosage change necessary**	✓	⚠ ↑ 60% in AUC ↑ 50% in C_{max}
Dronedarone	**Pharmacokinetic interaction** Inhibition of CYP3A4 (moderate) and P-gp (strong)	⚠ ↑ 40% in AUC ↑ 30% in C_{max} Data extrapolated from data on diltiazem (according to product monograph)	⚠ ↑ 85% in AUC ↑ 46% in C_{max} **Reduce edoxaban dosage to 30 mg daily**	⚠ No data	✗ ↑ 114-136% in AUC ↑ 87-125% in C_{max}
Quinidine	**Pharmacokinetic interaction** Inhibition of P-gp (moderate)	⚠ No data	⚠ ↑ 77% in AUC ↑ 85% in C_{max} **Reduce edoxaban dosage to 30 mg daily**	⚠ No data	⚠ ↑ 53% in exposure **Administer dabigatran at least 2 hrs before quinidine in patients with AF**
BETA-BLOCKERS					
Atenolol	**Pharmacokinetic interaction** ↑ gastric pH	✓ ↓ 15% in AUC ↓ 18% in C_{max}	✓ No data	✓ No data	✓ No data
Other beta-blockers	**Pharmacokinetic interaction** ↑ gastric pH	✓ No data	✓ No data	✓ No data	✓ No data
CARDIOTONIC GLYCOSIDES					
Digoxin	**Pharmacokinetic interaction** P-gp substrate	✓ No effect on bioavailability or pharmacokinetics	⚠ ↑ 17% in C_{max} of edoxaban ↑ 28% in C_{max} of digoxin **No dosage change necessary**	✓	✓
LIPID-LOWERING AGENTS					
Atorvastatin	**Pharmacokinetic interaction** CYP3A4 and P-gp substrate	✓ No data	✓ ↓ 15% in AUC or C_{max}	✓	✓ ↓ 20%
Lovastatin	**Pharmacokinetic interaction** CYP3A4 and P-gp substrate	✓ No data	✓ No data	✓ No data	✓ No data
Simvastatin	**Pharmacokinetic interaction** CYP3A4 and P-gp substrate	✓ No data	✓ No data	✓ No data	✓ No data

5 CARDIOVASCULAR SYSTEM (CONT'D)

Back

Concomitant drug	Mechanism	Apixaban (CYP3A4 and P-gp substrate)	Edoxaban (P-gp substrate)	Rivaroxaban (CYP3A4 and P-gp substrate)	Dabigatran (P-gp substrate)
SELECTIVE CALCIUM CHANNEL BLOCKERS					
Diltiazem	**Pharmacokinetic interaction** P-gp inhibition	↑ 40% in AUC ↑ 30% in C_{max} **No dosage change necessary**	No data	No data	No data
Verapamil	**Pharmacokinetic interaction** P-gp inhibition	No data	↑ 50% in AUC and C_{max} of edoxaban ↑ 14-16% in AUC and C_{max} of verapamil **No dosage change necessary**	No data	↑ 20-150% in AUC ↑ 10-180% in C_{max} **Administer dabigatran at least 2 hrs before verapamil**

6 MUSCULOSKELETAL SYSTEM

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Concomitant drug	Mechanism	Apixaban (CYP3A4 and P-gp substrate)	Edoxaban (P-gp substrate)	Rivaroxaban (CYP3A4 and P-gp substrate)	Dabigatran (P-gp substrate)
NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)					
Diclofenac	**Pharmacodynamic interaction** ↑ bleeding risk	No data	No data	No data	No effect on pharmacokinetics **No dosage change necessary**
Naproxen	**Pharmacokinetic and pharmacodynamic interaction** P-gp inhibition and ↑ bleeding risk	↑ 50% in AUC ↑ 60% in C_{max} **No dosage change necessary**	No effect on AUC or C_{max}	No effect on bioavailability or pharmacokinetics	No data
Other NSAIDs	**Pharmacodynamic interaction** ↑ bleeding risk	No data	No data	No data	No data

❼ NERVOUS SYSTEM

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Concomitant drug	Mechanism	Apixaban (CYP3A4 and P-gp substrate)	Edoxaban (P-gp substrate)	Rivaroxaban (CYP3A4 and P-gp substrate)	Dabigatran (P-gp substrate)
ANTIDEPRESSANTS					
Selective serotonin reuptake inhibitors (SSRIs)	Pharmacodynamic interaction ↑ bleeding risk	⚠ No data	⚠ No data	⚠ No data	⚠
Selective serotonin-norepinephrine reuptake inhibitors (SNRIs)	Pharmacodynamic interaction ↑ bleeding risk	⚠ No data	⚠ No data	⚠ No data	⚠
Vilazodone	Pharmacodynamic interaction ↑ bleeding risk	⚠ No data	⚠ No data	⚠ No data	⚠ No data
Vortioxetine	Pharmacodynamic interaction ↑ bleeding risk	⚠ No data	⚠ No data	⚠ No data	⚠ No data
ANTIEPILEPTICS					
Carbamazepine	Pharmacokinetic interaction Strong CYP3A4 and P-gp induction	✖	✖	✖	✖
Phenobarbital	Pharmacokinetic interaction Strong CYP3A4 and P-gp induction	✖	✖	✖	✖
Primidone	Pharmacokinetic interaction Strong CYP3A4 and P-gp induction	✖	✖	✖	✖
Phenytoin	Pharmacokinetic interaction Strong CYP3A4 and P-gp induction	✖	✖	✖	✖

❽ OTHERS

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Concomitant drug	Mechanism	Apixaban (CYP3A4 and P-gp substrate)	Edoxaban (P-gp substrate)	Rivaroxaban (CYP3A4 and P-gp substrate)	Dabigatran (P-gp substrate)
FOODS AND NATURAL PRODUCTS					
Grapefruit juice	Pharmacokinetic interaction Moderate CYP3A4 inhibition	⚠ No data	✔ No data	⚠ No data	✔ No data
St. John's wort	Pharmacokinetic interaction Strong CYP3A4 and P-gp induction	✖ Can cause a ↓ in the plasma concentration	✖ No data	✖ Can cause a ↓ in the plasma concentration	✖ No data