North Central London
Joint Formulary Committee

Direct Oral Anticoagulant (DOAC) Interactions

Disclaimer

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While we have tried to compile accurate information in this guideline, and to keep it updated in a timely manner, we cannot guarantee that it is fully complete and correct at all times. If you identify information within this guideline that is inaccurate, please report this to the admin.ncl-mon@nhs.net. If a patient is harmed as a consequence of following this guideline, please complete a local incident report and inform admin.ncl-mon@nhs.net.

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NCL JFC is funded by and provides advice to Acute Trusts and Clinical Commissioning Groups in NCL.

Document control

Date	Version	Amendments
17May17	1	New Document
21Aug18	1.1	Include 'Table of contents'

Document management

Groups / Individuals who have overseen the development of this guidance:	C Gates, Thrombosis and Anticoagulation Pharmacist, UCLH. J Minshull, JFC Support Pharmacist, NCL
Groups which were consulted and have given approval:	NCL Medicines Optimisation Committee
File name:	DOAC Interactions Guide
Version number:	1.1
Available on:	https://www.ncl-mon.nhs.uk
Disseminated to:	NCL Heads of Medicines Management, NCL Trust Formulary Pharmacists, NCL DOAC Stakeholder Group
Equality impact assessment:	Low
NCL Joint Formulary Committee Approval date:	August 2018 (MOC Chair's Action)
Review date:	May 2019

Contents

Pharmacokinetic data (DOACs)

Apixaban	Dabigatran etexilate	Edoxaban	Rivaroxaban
• Bioavailability approx. 50% • % of administered dose renally eliminated: 27% • Tmax 3-4h • $T_{1/2}$ 12h	• Bioavailability approx. 7% • % of administered dose renally eliminated: 85% • Tmax 0.5-2h • T ½ 12-14h (CrCL>80ml/min)	• Bioavailability approx. 62% • % of administered dose renally eliminated: 35% • Tmax 1-2h • T ½ 10-14h	• Bioavailability approx. 66% without food[a]; ≥80% with food[a,b] • % of administered dose renally eliminated: 66% (1/2 as unchanged active drug ie 33%) • Tmax 2-4h • T ½ 5-9h young; 11-13h elderly
• Mainly metabolized by CYP3A4/5 • Substrate of efflux transport proteins P-gp and breast cancer resistance protein (BCRP) • Not expected to inhibit / induce major CYP isoforms (e.g. CYP3A4). • Not a significant inhibitor of P-gp • **Affected by drugs that are strong inhibitors/inducers of both CYP3A4 and P-gp pathways**	• Not metabolised by the CYP450 system; not expected to induce/inhibit it • Dabigatran etexilate is a substrate of the efflux transport protein P-gp. • A**ffected by strong P-gp inhibitors or inducers**	• CYP3A4/5 weakly involved with metabolism (<10%) • Substrate of the efflux transport protein P-gp • Dose adjustment not needed for strong CYP3A4 inhibitors • **Affected by strong P-gp inhibitors or inducers**	• Metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms • Substrate of efflux transport proteins P-gp and breast cancer resistance protein (BCRP) • Does not inhibit / induce major CYP isoforms (e.g. CYP3A4) • **Affected by drugs that are strong inhibitors/inducers of both CYP3A4 and P-gp pathways**

Abbreviations: P-gp, P-glycoprotein. Footnote: [a] 20 mg dose; [b] 15mg/20 mg doses. Reference: Summary Product Characteristics www.medicines.org.uk; Heidbuchel et al. Updated EHRA practical guide on the use of non-VKA AC in NVAF: Executive summary—Revision 1. EHJ 2016 doi:10.1093/eurheartj/ehw058

Drug interactions with DOACs (therapeutic doses)

Disclaimer

- Available data is limited and may change as DOACs become more widely prescribed.
- Absence of an individual drug/specific recommendation or information does not translate into safety for use.
- The suggested actions are a combination of SPC advice, EHRA practical guidance (see references) and local interpretation.
- Refer to the relevant SPC/BNF for the most-up-to date information when prescribing https://www.medicines.org.uk/emc/
- Where stated, 'AUC' relates to DOAC concentration

Interaction table

Clinical risk factors for bleeding		Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Additional risk factors that will or may increase the risk of bleeding, in addition to any of the potential drug interactions listed below (NB: not exhaustive)		≥ 80yrs	≥ 75yrs	Elderly	Elderly
		≤ 60kg	≤ 50kg	≤ 60kg	≤ 50kg
		Cr >133µmol/L, CrCL 30-50mL/min	moderate renal imp (CrCL 30-50mL/min)	moderate renal imp (CrCL 30-50 mL/min)	moderate renal imp (CrCL 30 - 50 ml/min)
			gastritis, oesophagitis, GORD	gastritis, oesophagitis, GORD	gastritis, oesophagitis, GORD
		History of GI bleeding; recent surgery on critical organ; thrombocytopenia; HASBLED ≥ 3			
Interacting drug factors	**Mechanism**	**Apixaban**	**Dabigatran**	**Edoxaban**	**Rivaroxaban**
Antiarrhythmics					
Amiodarone *Note **long half-life of amiodarone**; any drug interaction may persist for some weeks after stopping amiodarone*	Moderate CYP3A4 and mild-mod P-gp inhibitor	Caution	↑ AUC 60%. Caution and close clinical surveillance required specially in mild-mod renal imp or other 'yellow' risk factors - consider lower dose. *(NB: different advice for orthopaedic VTE prophylaxis: see SPC)*	↑ AUC 40%	Not listed in SPC Caution
Digoxin	P-gp substrate	No interaction	No interaction	Not clinically relevant	Not clinically relevant
Diltiazem	Moderate CYP3A4 and weak P-gp inhibitor	↑ AUC 1.4 fold Caution	Not listed in SPC; significant interaction not expected	Not listed in SPC; significant interaction not expected	Not listed in SPC; significant interaction not expected. Caution in renal impairment

Antiarrhythmics continued overleaf

Key

Red box, white text	Yellow box, black text	Purple box, white text	White box, black text	Blue box, white text
Contraindicated / avoid / not recommended	**Caution use / monitor closely** *(note: If ≥2 yellow factors are present, consider alternative drug / seek advice)*	**Reduce dose as per SPC** *(caution use / monitor closely if additional yellow factors present; consider alternative / seek advice)*	**No or limited data / not listed in SPC / unable to advise** *(unless otherwise stated)*	**No clinically meaningful interaction expected**

- **Renal impairment:** SPCs for DOAC classify renal impairment (CrCL, Cockcroft Gault) as follows: **Mild: 50-80mL/min; Mod: 30-50mL/min; Severe: <30mL/min** (this may differ from the classification of renal impairment in the BNF)
- ***NOTE:*** *Dabigatran is contraindicated with severe renal failure (CrCL <30mL/min); NCL advises against the use of apixaban/edoxaban/rivaroxaban with CrCL 15-30mL/min unless discussed with haematologist.*

Interacting drug	Mechanism via	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Antiarrhythmics contd.					
Dronedarone	Moderate CYP3A4 and strong P-gp inhibitor	Not listed in SPC; Note advice to *avoid* with rivaroxaban. NCL advice: avoid	↑AUC 90-125% Contraindicated	↑AUC 85% ↓30mg OD and caution with additional yellow risk factors	Limited clinical data Avoid
Verapamil	Moderate CYP3A4 and mild-mod P-gp inhibitor	Caution	↑ AUC ~ 50-150%. ↓110mg bd and take at same time of day. Caution with additional yellow risk factors and r/v choice. *(NB: different advice for orthopaedic VTE prophylaxis: see SPC)*	↑ AUC 53% Caution	Not listed in SPC caution
Antibiotics					
Clarithromycin	Strong CYP3A4 and moderate P-gp inhibitor	Not listed in SPC; clinically relevant interaction not expected Caution in renal impairment	SPC: interaction cannot be excluded; close monitoring	Not listed in SPC; Caution and note interaction with erythromycin and the recommendation to ↓dose	Not considered clinically relevant SPC advises caution in renal impairment
Erythromycin	Moderate CYP3A4 and moderate P-gp inhibitor	Not listed in SPC; clinically relevant interaction not expected	Not listed in SPC; note comment with clarithromycin	↑AUC 85% ↓30mg OD and caution with additional yellow risk factors	Not considered clinically relevant SPC advises caution in renal impairment
Rifampicin	Strong inducer of both CYP3A4 and P-gp	May ↓AUC 54% - Avoid	↓AUC 66-67% - Avoid	May ↓AUC - Avoid	↓AUC 50% - Avoid
Anticoagulants					
Heparin, LMWH (e.g. dalteparin, enoxaparin, tinzaparin), fondaparinux, warfarin, DOACs		Combination contraindicated except when switching therapy to or from DOAC (as advised by A/C clinic or haemostasis SpR/Cons), or when unfractionated heparin is given at doses necessary to maintain a patent central venous or arterial catheter			
Antidepressants					
SSRIs (Selective serotonin re-uptake inhibitors) / **SNRIs** (selective norepineph. re-uptake inhibitors)	Pharmacodynamic	Consider GI cover if other risk factors for bleeding present	Consider GI cover if other risk factors for bleeding present and consider ↓ 110mg bd	Consider GI cover if other risk factors for bleeding present	Consider GI cover if other risk factors for bleeding present

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Contraindicated / avoid / not recommended	**Caution use / monitor closely** *(note: If ≥2 yellow factors are present, consider alternative drug / seek advice)*	**Reduce dose as per SPC** *(caution use / monitor closely if additional yellow factors present; consider alternative / seek advice)*	**No or limited data / not listed in SPC / unable to advise** *(unless otherwise stated)*	**No clinically meaningful interaction expected**

- **Renal impairment:** SPCs for DOAC classify renal impairment (CrCL, Cockcroft Gault) as follows: **Mild: 50-80mL/min; Mod: 30-50mL/min; Severe: <30mL/min** (this may differ from the classification of renal impairment in the BNF)
- ***NOTE:*** *Dabigatran is contraindicated with severe renal failure (CrCL <30mL/min); NCL advises against the use of apixaban/edoxaban/rivaroxaban with CrCL 15-30mL/min unless discussed with haematologist.*

Interacting drug factors	Mechanism	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Anti-inflammatory agents					
NSAIDs *(Non-steroidal anti-inflammatory drugs)*	Pharmacodynamic	**Increased risk of bleeding. Stop/avoid if at all possible**. Careful risk-benefit assessment required. If benefit of chronic NSAID outweighs risk of bleeding then **(1) review the most appropriate drug combination and dose (2) PPI cover strongly advised**. **Close clinical monitoring required** *(NB: SPC for edoxaban specifically states chronic NSAID use not recommended)*			
Prednisolone	Pharmacodynamic	Increased risk of bleeding. Consider GI cover if additional risk factors present			
Antiplatelet agents					
Aspirin / clopidogrel	Pharmacodynamic	**Increased risk of major bleeding**: **Stop antiplatelet agent** UNLESS another specific clinical indication (other than AF) exists. If concomitant therapy unavoidable (and a careful risk-benefit assessment has been made) then **(1) review the most appropriate drug combination and dose; (2) PPI cover strongly advised**. **Close clinical monitoring required**			
Ticagrelor	Mild CYP3A4 and mild-mod P-gp inhibitor; pharmacodynamic	**Potent antiplatelet agents**; clinical data for concurrent use lacking; **very high risk of major bleeding expected**. *(Ticagrelor ↑ AUC and Cmax of dabigatran, extent depends on dosing regimen; see SPC)* NCL: Avoid			
Prasugrel	Pharmacodynamic				
Antivirals					
HIV protease inhibitors e.g. ritonavir	Strong inhibitor of CYP3A4; strong P-gp inhibitor / inducer	Avoid	Not been studied - avoid	Not been studied - avoid	Ritonavir ↑ AUC 2.5 fold Avoid
HIV medication - other		Check specialist HIV drug interaction sites			

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- **Renal impairment: SPCs for DOAC classify renal impairment (CrCL, Cockcroft Gault) as follows: Mild: 50-80mL/min; Mod: 30-50mL/min; Severe: <30mL/min** (this may differ from the classification of renal impairment in the BNF)
- ***NOTE:*** *Dabigatran is contraindicated with severe renal failure (CrCL <30mL/min); NCL advises against the use of apixaban/edoxaban/rivaroxaban with CrCL 15-30mL/min unless discussed with haematologist*

Interacting drug	Mechanism via	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Azole antimycotics (systemic)					
Itraconazole Ketoconazole Voriconazole Posaconazole	Strong inhibitors of both CYP3A4 and P-gp *(posaconazole considered strong CYP3A4 / mod P-gp inhibitor)*	Ketoconazole ↑ AUC 2-fold Avoid with all	Ketoconazole (↑AUC 150%) and itraconazole - both contraindicated Voriconazole not in SPC. Avoid Posaconazole - no clinical data; caution. (If mild-mod renal imp, ≥75yrs or ≤ 50kg, then avoid)	Ketoconazole ↑AUC 87% ↓30mg OD and caution with additional yellow risk factors Itraconazole, voriconazole and posaconazole are not listed in SPC; interaction expected; seek advice	Ketoconazole ↑ AUC 2.6 fold Avoid with all
Fluconazole	Moderate CYP3A4 inhibitor	Not listed in SPC; clinically relevant interaction not expected Caution in renal impairment	Not listed in SPC; interaction unlikely	Not listed in SPC; interaction unlikely	Not considered clinically relevant SPC advises caution in renal impairment
GI protection					
Proton pump inhibitors		Not listed in SPC; not expected to be clinically relevant	Not clinically relevant	Not clinically relevant	Omeprazole; no clinically significant interaction
Ranitidine / famotidine		Not clinically relevant	Not clinically relevant	Interaction unlikely	Interaction unlikely
Immunosuppressants					
Ciclosporin	Moderate CYP3A4 and strong P-gp inhibitor	Not listed in SPC; extent of interaction unknown; seek advice	Contraindicated	↑AUC 73% ↓30mg OD and caution with additional yellow risk factors	Not listed in SPC; extent of interaction unknown; seek advice
Tacrolimus	CYP3A4 and mod-strong P-gp inhibitor	Not listed in SPC; extent of interaction unknown; seek advice	No clinical data Avoid	Not listed in SPC; interaction expected; Avoid	Not listed in SPC; extent of interaction unknown; seek advice

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- ***NOTE:*** *Dabigatran is contraindicated with severe renal failure (CrCL <30mL/min); NCL advises against the use of apixaban/edoxaban/rivaroxaban with CrCL 15-30mL/min unless discussed with haematologist.*

Interacting drug factors	Mechanism	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Others					
Atorvastatin	Substrate of CYP3A4; weak P-gp inhibitor	Not listed in SPC; interaction unlikely	No interaction	Not listed in SPC; interaction not expected	No clinically significant interaction
Simvastatin	Substrate of CYP3A4; some P-gp inhibition	Not listed in SPC; interaction unlikely	Not listed in SPC; early signal suggests ↑bleeding risk, but full extent of possible interaction unknown (seek advice)	Not listed in SPC; unable to comment	Not listed in SPC; clinically significant interaction not expected
Phenytoin Carbamazepine Phenobarbitone St. John's Wort *(Hypericum perforatum)*	Strong inducers of both CYP3A4 and P-gp	May ↓ AUC ~50% Avoid	↓ plasma levels expected: avoid *(NB: SPC does not specifically mention phenobarbitone)*	May ↓ AUC Avoid	Avoid
		Note that any interaction may persist for some weeks after discontinuation of the inducing drug			
Thrombolytic agents, GPIIb/IIIa receptor antagonists					
		Urgently d/w haematology consultant should the situation arise			

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