Common drug interactions with DOACs

Interacting drug	Pharmacokinetic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
DOACs mechanism of interaction		**Affected by strong P-gp inhibitors or inducers[1]**	**Affected by drugs that are strong inhibitors/inducers of both CYP3A4 and P-gp pathways[1]**	**Affected by drugs that are strong inhibitors/inducers of both CYP3A4 and P-gp pathways[1]**	**Affected by strong P-gp inhibitors or inducers[1]**
		NB: An important interaction mechanism for all DOACs consists of significant gastrointestinal re-secretion over a P-glycoprotein (P-gp) transporter after absorption in the gut. Competitive inhibition of this pathway will result in increased plasma levels. The P-gp transporter is also involved in renal clearance. CYP3A4-type cytochrome P450-dependent elimination is involved in the hepatic clearance of rivaroxaban and apixaban. Strong CYP3A4 inhibition or induction may affect plasma concentrations. In general, DOAC use is not recommended in combination with drugs that are strong inhibitors/ inducers of both CYP3A4 and P-gp.Such combinations should be avoided or used with great caution and surveillance [2]			
Antiarrhythmics					
Amiodarone ***NB**: due to the long half-life of amiodarone; any drug interaction may persist for some weeks after stopping amiodarone[3]*	Moderate CYP3A4 and mild to moderate P-glycoprotein (P-gp) inhibitor[1,4]	No dosage reduction ***Caution**: observe for signs of bleeding or anaemia, especially if other bleeding risk factors present (e.g. Age ≥ 75 years, 30-50 mL/min CrCl, low body weight (< 50 kg), diseases / procedures with special haemorrhagic risks or taking other cautioned medication.[3]*	Not documented in SPC[7] Effect considered minor, monitor for signs of bleeding[2]	No dose adjustment[5] Monitor patients for signs of bleeding[11]	No dose reduction[14]

Interacting drug	Pharmacokinetic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
		NB*: Dose reduction required for primary prevention of venous thromboembolism in orthopaedic surgery*[10]			
Digoxin	P-gp substrate[3]	No interaction[3]	Not documented in SPC[7] No dose adjustment needed[11]	No dose adjustment [5]	No dose reduction[14]
Diltiazem	Moderate CYP3A4 and weak P-gp inhibitor[5]	Not listed in SPC[3] No significant interaction expected[2]	Not documented in SPC[7] No effect[2]	No dose adjustment[5] Monitor patients for signs of bleeding[11]	Not documented in SPC[14] No data[2]
Dronederone	Moderate CYP3A4 and strong P-gp inhibitor[6]	Contraindicated[3]	Avoid concomitant use[7]	Not documented in SPC[5] Predicted to increase the exposure to apixaban. Monitor patients for signs of bleeding[11]	Dose reduction to 30mg once daily[14]
Quinidine	Mild to moderate P-gp inhibitor[3]	No dosage reduction ***Caution****: observe for signs of bleeding or anaemia, especially if other bleeding risk factors present (e.g. Age ≥ 75 years, 30-50 mL/min CrCl, low body weight (< 50 kg), diseases / procedures with special*	Not documented in SPC[7] Extend on plasmaconcentration of rivaroxaban unknown[2]	No dose adjustment[5] Monitor patients for signs of bleeding[11]	No dose reduction. Monitor for signs of bleeding[14]

Interacting drug	Pharmacokinetic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
		haemorrhagic risks or taking other cautioned medication.[3] NB*: Dose reduction required for primary prevention of venous thromboembolism in orthopaedic surgery*[10]			
Verapamil	Moderate CYP3A4 and mild to moderate P-gp inhibitor[1]	Dose reduction to 110mg twice daily ***NB**: advice to take at the same time* ***Caution**: observe for signs of bleeding or anaemia, especially if other bleeding risk factors present (e.g. Age ≥ 75 years, 30-50 mL/min CrCl, Low body weight (< 50 kg), Diseases / procedures with special haemorrhagic risks or taking other cautioned medication.*[3] ***NB:** Dose reduction required for primary prevention of venous thromboembolism in orthopaedic surgery*[10]	Not documented in SPC[7]	No dose adjustment[5] Monitor patients for signs of bleeding[11]	No dose reduction. Monitor for signs of bleeding[14]

Interacting drug	Pharmacokinetic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Antivirals					
HIV protease inhibitors (e.g. ritonavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir)	Strong inhibitor of CYP3A4; strong P-gp inhibitor / inducer[1]	Not recommended- avoid - as not studied[3]	Concomitant use not recommended[7]	Concomitant use not recommended[5]	Not studied, no data[2,14]
Antifungals					
Itraconazole	Strong inhibitors of both CYP3A4 and P-gp[1,3] (Posaconazole considered strong CYP3A4 / moderate P-gp inhibitor[1])	Contra-indicated[3]	Concomitant use not recommended[7]	Concomitant use not recommended[5]	Not documented in SPC[14] Interaction expected Predicted to increase the exposure to edoxaban[11]
Voriconazole		Not in SPC – avoid) Not recommended[2]	Concomitant use not recommended[7]	Concomitant use not recommended[5]	
Posaconazole		No clinical data - Use with caution[3]	Concomitant use not recommended[7]	Concomitant use not recommended[5]	
Ketoconazole		Contra-indicated[3]	Concomitant use not recommended	Concomitant use not recommended[5]	Dose reduction to 30mg once daily[14]
Fluconazole	Moderate CYP3A4 inhibitor[2]	No data[2]	Interaction not considered clinically relevant. No dose reduction required[11] ***NB**: Interaction potentially signifant in high-risk patients (e.g. renal impairment), use with caution ,especially in patient with renal impairment and concomitantly receiving other drugs which may*	Interaction not considered clinically relevant. No dose reduction required[11]	No data[2]

Interacting drug	Pharmacokinetic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
			increase rivaroxaban plasma concentration.[7]		
Antibiotics					
Clarithromycin	Strong CYP3A4 and moderate P-gp inhibitor[2]	No dosage reduction ***NB**: Close observation for signs of bleeding or anaemia is recommended throughout treatment period, especially if other bleeding risk factors present (e.g. Age ≥ 75 years, 30-50 mL/min CrCl, Low body weight (< 50 kg), Diseases / procedures with special haemorrhagic risks or taking other cautioned medication.*[3]	Not considered clinically relevant interaction ***NB**: The interaction is potentially significant for high-risk patients e.g.patients with severe renal impairment (creatinine clearance < 30 ml/min) as rivaroxaban plasma levels may be significantly increased which may lead to an increased bleeding risk, those with conditions with increased risk of haemorrhage, increasing age, other haemorrhagic risk factors*[7]	No dose adjustment[5] Monitor for/advise patients on signs of bleeding[11] Expected increase in plasma concentration of apixaban[13]	Not in SPC[14] Predicted to increase the exposure to edoxaban. Monitor patients for signs of bleeding[11]

Interacting drug	Pharmacokinetic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Erythromycin	Moderate CYP3A4 and moderate P-gp inhibitor[7]	Not in SPC[3] Predicted to increase the exposure to dabigatran. Monitor patients for signs of bleeding[11]	Not considered clinically relevant interaction ***NB**: as per the comment for clarithromycin, the interaction is potentially significant for high-risk patients.* *The effect of erythromycin is additive to that of renal impairment[7]*	Not in SPC[5] Might increase exposure to apixaban. Monitor patients for signs of bleeding[11]	Dose reduction to 30mg once daily[14]
Rifampicin	Strong CYP3A4 inducer[7] and P-gp inducer[3]	Avoid concomitant use[3] ***NB:** combination leads to decrease in anticoagulant effect; the interaction is diminished 7 days after stopping rifampicin[11]*	Avoid concomitant use[7]	Avoid concomitant use[13] ***NB**: SPC notes that for prevention of stroke and systemic embolism NVAF and prevention of recurrent DVT and PE :use rifampicin with caution. For treatment of DVT and treatment of PE: do not use[5]*	Use with caution[14]
Gastro-protection					
PPIs		No clinically relevant interaction, no dose reduction required[3]	No clinically significant interaction observed[7]	Not documented in SPC[5] No clinically relevant interaction expected[2]	No impact on edoxaban exposure[14]

Interacting drug	Pharmacokinetic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Immunosuppresants					
Ciclosporin	Moderate CYP3A4 inhibitor, strong P-gp inhibitor[3]	Contra-indicated[3]	Not documented in SPC[7] Predicted to increase the exposure to rivaroxaban, increasing its effects. Monitor patients for signs of bleeding[11]	Not documented in SPC[5] Predicted to increase the exposure to apixaban, increasing its effects. Monitor patients for signs of bleeding11	Dose reduction to 30mg once daily[14]
Tacrolimus	CYP3A4 inhibitor, strong to moderate P-gp inhibitor[2]	Concomitant use not recommended[3]	Not documented in SPC[7] Extend of interaction unknown[2]	Not documented in SPC[5] Extend of interaction unknown[2]	Not documented in SPC[14] Interaction expected. Avoid.[1]
Anti-epileptics					
Phenytoin	Strong inducers of both CYP3A4 and P-gp[2]	Avoid concomitant use[3]	Avoid concomitant use[7]	Avoid concomitant use[13] ***NB**: SPC notes* *- Prevention of stroke and systemic embolism NVAF and prevention of recurrent DVT and PE: use with caution;* *- Treatment of DVT and treatment of PE: not to be used[5]*	Use with caution[14]

Interacting drug	Pharmacokinetic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Carbamazepine	Strong inducers of both CYP3A4 and P-gp[2]	Avoid concomitant use[3]	Avoid concomitant use[7]	Avoid concomitant use[13] ***NB**: SPC notes* *- Prevention of stroke and systemic embolism NVAF and prevention of recurrent DVT and PE: use with caution;* *- Treatment of DVT and treatment of PE: not to be used[5]*	Use with caution[14]
Phenobarbitone	Strong inducers of both CYP3A4 and P-gp[2]	Not documented in SPC[3] Concomitant use should be avoided[2]	Avoid concomitant use[7]	Avoid concomitant use[13] ***NB**: SPC notes* *- Prevention of stroke and systemic embolism NVAF and prevention of recurrent DVT and PE: use with caution;* *- Treatment of DVT and treatment of PE: not to be used[5]*	Use with caution[14]

Interacting drug	Pharmacodynamic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Anti-inflammatory drugs					
NSAIDs	Increased bleeding risk[2] **NB**: NSAID considerations: - continued need? - lowest dose and shortest duration - gastroprotection[8]	Use with caution[3] Avoid concomitant use if possible[9] Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk *(e.g. Age ≥ 75 years, 30-50 mL/min CrCl, low body weight (< 50 kg), diseases / procedures with special haemorrhagic risks or taking other cautioned medication).[3]*	Use with caution[7] Avoid concomitant use if possible[12] Monitor for signs of bleeding[7] Review benefits vs. risks, considering other factors contributing to increased bleeding risk[7]	Use with caution[5] Avoid concomitant use if possible[13] Monitor for signs of bleeding[5] Review benefits vs. risks, considering other factors contributing to increased bleeding risk[5]	Use with caution, Avoid concomitant use if possible (chronic use is not recommended[14] Monitor for signs of bleeding[14] Review benefits vs. risks, considering other factors contributing to increased bleeding risk[14]
Antiplatelet agents					
Aspirin/Clopidogrel	Increased bleeding risk[2] **NB:** Review need for antiplatelet therapy to continue**.** Avoid concomitant use[9] unless necessary (e.g. dual/triple therapy post ACS/PCI – seek	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk

Interacting drug	Pharmacodynamic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
	cardiologist advice and determine duration of dual/triple therapy) **NB**: Gastroprotection indicated	*(e.g. Age ≥ 75 years, 30-50 mL/min CrCl, low body weight (< 50 kg), diseases / procedures with special haemorrhagic risks or taking other cautioned medication).*[3]			Low dose aspirin: Use with caution[14]
Prasugel	Increased bleeding risk Assess risk/benefit in each clinical situation[2]	Limited experience /evidence[3] Concomitant use should be avoided[5] ***NB:*** *only on advice of cardiologist should dual therapy with prasugel be indicated*[2]	Manufacturer advises use with caution[7] or avoid[12] ***NB:*** *only on advice of cardiologist should dual therapy with prasugel be indicated*[2]	Use with caution or avoid[5,13] ***NB:*** *only on advice of cardiologist should dual therapy with prasugel be indicated*[2]	Use with caution or avoid[14] ***NB:*** *only on advice of cardiologist should dual therapy with prasugel be indicated*[2]
Ticagrelor	Increased bleeding risk[2] Assess risk/benefit in each individual clinical situation[2] **NB**: Pharmacokinetic interaction: mild inhibitor of CYP3A4, P-gp, substrate, Mild to moderate P-gp inhibitor[3]	Manufacturer advises use with caution as limited data[3] ***NB:*** *only on advice of cardiologist should dual therapy with ticagrelor be indicated*[2]	Manufacturer advises use with caution[7] or avoid[12] ***NB:*** *only on advice of cardiologist should dual therapy with ticagrelor be indicated*[2]	Use with caution or avoid[5,13] ***NB:*** *only on advice of cardiologist should dual therapy with ticagrelor be indicated*[2]	Use with caution or avoid[14] ***NB:*** *only on advice of cardiologist should dual therapy with ticagrelor be indicated*[2]

Interacting drug	Pharmacodynamic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Antidepressants					
SSRIs/SNRIs	Increased bleeding risk ***NB**: review if gastro-protection is indicated*	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk *(e.g. Age ≥ 75 years, 30-50 mL/min CrCl, Low body weight (< 50 kg), diseases / procedures with special haemorrhagic risks or taking other cautioned medication).*[3]	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk
St Johns Wort	Pharmacokinetic interaction: potent CYP3A4 and P-gp inducer[2]	Avoid concomitant use[3]	Avoid concomitant use[7]	Avoid concomitant use[13] ***NB**: SPC notes* *-Prevention of stroke and systemic embolism NVAF and prevention of recurrent DVT and PE: use with caution;* *-Treatment of DVT and treatment of PE: not to be used*[5]	Use with caution[14]

Disclaimer:

Data on drug interactions with DOACs is still limited albeit information is expanding, the availability of new information may modifiy current guidance. The information is based on reference sources cited and interpretation/experience of heath care professionsals involved in producing and reviewing this document. The interaction document is intended for guidance only to support individual clinical decisions when prescribing DOAC therapy in combination with other drugs. The authors and EoE Pac accept no liability. Please use in conjunction with the relevant SPC's available via www.medicines.org.uk

The guide describes the effect of the interacting drug on the relevant DOAC.

When prescribing a DOAC in combination with other medication, it is important to consider the pharmacokinetic/dynamic interactions as well as a patient's comorbidities and other factors contributing to an increased bleeding risk (such as age, renal function, low body weight)[2] The guide aims to provide a quick reference for primary care clinicians, firm dosage reductions have only been advised where this is in accordance with the product licensing. If after reviewing the drug interactions, co-morbities and other patient factors, it is considered an unlicensed DOAC dosage reduction or increase is required, then specialist advice should be sought and the reason for the dosage reduction or increase should clearly be documented in the patients notes.

Colour code:

	Indicates contra-indication or strong recommendation to avoid concomitant use
	Indicates strong recommendation of caution (e.g. may require use with caution in all circumstances, requires dose reduction, notes additional warnings in specific conditions or the EoE PAC considers it warrants an amber recommendation based on experience/interpretation)
	Requires assessement of additive effect of drug-interactions, co-morbidities and other patient factors to make informed clinical decision

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Version	2.0 Harmonisation of West Essex guidance and HMMC guidance, updates include: • Rebadged from HVCCG, ENHCCG and WECCG to HWE ICB • Replaced NOAC with DOAC, current accepted naming convention • Remove footer and version control box added
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Review date	This recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.