Comparison of DOACs for Non-valvular Atrial Fibrillation

Information for prescribers

June 2022

	Apixaban	Dabigatran etexilate (as mesilate)	Edoxaban	Rivaroxaban ▼
Brand Name	Eliquis	Pradaxa	Lixiana	Xarelto
Presentation	2.5mg and 5mg film coated tablets	110mg and 150mg hard capsules NB. 75mg capsules are not licensed for AF.	15mg, 30mg and 60mg film coated tablets	15mg and 20mg film coated tablets NB. 1 mg/mL granules for oral suspension, 10mg and 2.5mg tablets are not licensed for AF.
Licensed indication	All DOACS are licensed for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure (NYHA Class ≥ II stated for apixaban and dabigatran), hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. All four DOACS are licensed and have trial evidence of efficacy and safety in use for patients undergoing direct current cardioversions. (Rivaroxaban – X-VERT/ARC; ENSURE-AF-Edoxaban; NCT01593150-Dabigatran; EMANATE-Apixaban).			
Relative efficacy	There are currently no head-to-head Randomised Controlled Trials (RCTs) that directly compare DOACs against each other. Network meta-analyses (NMAs) have been published, incorporating RCTs and observational studies with various methodologies. These have limitations given the heterogeneity of the different trials, however they do allow some comparison of the DOACs to aid clinical decision making. In patients with NVAF there is not one DOAC suitable for all patients. Choice should be based on a range of factors including co-morbidities and patient preference. Where there is no clinical reason to use a specific DOAC, and due to the National Procurement for DOACs scheme clinicians are encouraged to use the DOAC with the lowest acquisition cost, which is currently edoxaban. All DOACs are shown to be non-inferior (or superior in the case of apixaban and dabigatran 150mg) to warfarin for stroke prevention in AF. A meta-analysis showed all high dose DOACs have comparable efficacy for the composite primary and bleeding outcomes. Major bleeding rates were significantly lower for edoxaban and apixaban compared to warfarin than those seen with dabigatran and rivaroxaban.			
Licensed doses for stroke prevention in NVAF	5mg TWICE daily	150mg TWICE daily The dosing interval should be as close to 12 hours as possible.	60mg ONCE daily	20 mg ONCE daily with food. The tablets should be taken approximately 24 hours apart.
Reduced dose for stroke prevention in NVAF	2.5mg twice daily if 2 or more of the following present: age 80 years or older, body weight 60 kg or less or serum creatinine 133 micromole/L or greater OR 2.5mg twice daily where CrCl 15-29ml/min	110mg twice daily age 80 years or older or concomitant use of verapamil. Consider dose reduction from 150mg twice daily to 110mg twice daily in the following: age 75-80 years, moderate renal impairment (CrCl 30-50ml/min), patients with gastritis, oesophagitis or gastroesophageal reflux and other patients at increased risk of bleeding.	30mg once daily if one or more of the following present: body weight 60kg or less, CrCl 15-50ml/min or concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole.	15mg once daily where CrCl 15-49ml/min.

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Other licensed indications (may vary depending on formulation)	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Prevention of VTE post hip or knee replacement.	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age. Primary prevention of VTE in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Acute Coronary Syndrome. Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment.
Criteria for use in non-valvular AF	Presence of one or more of the following risk factors: • Prior stroke or transient ischaemic attack • Age 75 years or older • Hypertension • Diabetes mellitus • Congestive heart failure (NYHA Class 2 or above)	Presence of one or more of the following risk factors: • Prior stroke or transient ischaemic attack or systemic embolism • Age 75 years or older • Hypertension • Diabetes mellitus • Congestive heart failure (NYHA Class 2 or above)	Presence of one or more of the following risk factors: • Prior stroke or transient ischaemic attack • Age 75 years or older • Hypertension • Diabetes mellitus • Congestive heart failure	Presence of one or more of the following risk factors: • Prior stroke or transient ischaemic attack • Age 75 years or older • Hypertension • Diabetes mellitus • Congestive heart failure
Efficacy for stroke prevention	Superior to warfarin (ARISTOTLE trial) Note: Approximately 5% of the study population received 2.5 mg apixaban or placebo.	Superior to warfarin with 150 mg twice daily dose. Non-inferior to warfarin with 110 mg twice daily dose (RE-LY trial).	Non-inferior to warfarin (ENGAGE-AF TIMI 48 trial). Note: Approximately 25 % of population received 30 mg edoxaban.	Non-inferior to warfarin (ROCKET-AF trial). Note: Approximately 20 % of the population received 15 mg rivaroxaban.
Contraindications – all DOACs	• Hypersensitivity to the active substance or any of its excipients. • Clinically significant active bleeding • A lesion or condition, if considered a significant factor for major bleeding • Co-administration with other anticoagulants, except under specific circumstances (e.g. switching to warfarin). • Antiphospholipid syndrome; there is a risk of recurrent thrombotic events. See MHRA DSU.			

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Contraindications – drug Specific	• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. • Not recommended if CrCl <15ml/min. • Safety and efficacy of apixaban have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of apixaban is not recommended in this setting.	• Hepatic impairment or liver disease expected to have any impact on survival. • Contra-indicated if CrCl <30ml/min. • Prosthetic heart valves requiring anticoagulation. See MHRA DSU. • Concurrent treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporin, itraconazole, dronedarone.	• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. • Not recommended if CrCl <15ml/min. • There is a trend towards lower efficacy with increasing CrCl (vs. warfarin). Edoxaban should only be used in high CrCl after careful evaluation of the individual thromboembolic and bleeding risk. SPS suggest consider using another anticoagulant if CrCL >95ml/min. • Edoxaban has not been studied in patients with mechanical heart valves, in patients during the first 3 months after implantation of a bioprosthetic heart valve, with or without atrial fibrillation, or in patients with moderate to severe mitral stenosis. Therefore, use of edoxaban is not recommended in these patients. • Uncontrolled severe hypertension. • Pregnancy and breastfeeding.	• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including patients with Child Pugh B & C. • Not recommended if CrCl <15ml/min • Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients. • Transcatheter aortic valve replacement (TAVR). See MHRA DSU. • .Pregnancy and breastfeeding.
NICE recommendations	NICE TAs 249 (dabigatran), 256 (rivaroxaban), 275 (apixaban) and 355 (edoxaban) and NICE NG196 Atrial Fibrillation recommend the use of DOACs as first line treatment options for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF). NICE NG196 states to offer anticoagulation with a DOAC to people with NVAF who are not currently anticoagulated, have a CHA2DS2-VASc score of 2 or above for women and 1 or above for men, and considering the risk of bleeding.			
CAD, previous MI, or high risk for ACS/MI	Consider agent with a positive effect in ACS. *Rivaroxaban is the only licensed DOAC indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS). Please refer to posology section of rivaroxaban.*			
History of GI bleed or high risk	Consider agent with lowest reported GI bleeding outcomes or adverse effects. *In the clinical trials (RE-LY, Engage & Rocket) higher rates of GI bleeding were reported with dabigatran etexilate 150 mg, rivaroxaban, and edoxaban, compared to warfarin. Apixaban was associated with similar risks to warfarin in clinical trials (ARISTOTLE).*			

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Bleeding risk	Major bleeding: less common with apixaban than warfarin (p<0.001). GI bleeding: no difference between apixaban and warfarin. Intracranial bleeding: less common with apixaban than warfarin. (p<0.001)	Major bleeding: no difference between dabigatran 150mg BD and warfarin. Less common with dabigatran 110mg BD than warfarin. GI bleeding: more common with dabigatran 150mg BD than warfarin (p=0.0008). No difference between dabigatran 110mg BD and warfarin. Intracranial bleeding: less common with both doses of dabigatran than with warfarin (p<0.001). **Bleeding risk: high in frail/ elderly particularly with renal impairment and low weight.**	Major bleeding: significantly reduced rate of major bleeding and of several secondary bleeding endpoints for 60mg/30mg edoxaban compared to warfarin (p≤0.01). Major GI bleeding: occurred slightly more frequently in edoxaban 60mg/30mg than in warfarin (p=0.03). In clinical studies mucosal bleedings and anaemia were seen more frequently during long term edoxaban treatment compared with VKA treatment, therefore in addition to adequate clinical surveillance, laboratory testing of haemoglobin / haematocrit could be of value to detect occult bleeding.	Major bleeding: no difference between rivaroxaban and warfarin. GI bleeding: more common with rivaroxaban than warfarin (p<0.001). Approximately 88% of major bleeding episodes associated with rivaroxaban originate in GI tract. Intracranial bleeding: less common with rivaroxaban than warfarin (p=0.02).
Major bleed risk compared to warfarin	Reduced risk (NNT= 104, ARISTOTLE)	Similar risk with 150mg. Reduced risk with 110mg (NNT= 154, RE-LY)	Reduced risk (NNT 147, ENGAGE AF-TIMI 48)	Similar risk (ROCKET-AF)
Intracranial bleed risk compared to warfarin	Reduced risk (NNT=213, ARISTOTLE)	Reduced risk (NNT=228 with 150mg, 197 with 110mg, RE-LY)	Reduced risk (NNT 218, ENGAGE AF-TIMI 48)	Reduced risk (NNT=500, ROCKET-AF)
Gastrointestinal bleed risk compared to warfarin * Major GI bleeding	Similar risk (ARISTOTLE)	Increased risk * (NNH=204 with 150mg, RE-LY)	Increased risk * (NNH 358, ENGAGE AF-TIMI 48, Edoxaban 60mg)	Increased risk * (NNH 100, ROCKET-AF)
Dyspepsia incidence compared to warfarin	Not reported (ARISTOTLE)	Increased incidence (NNH=17 with 110mg, 18 with 150mg, RE-LY). Consider co-prescription of a PPI.	Not reported (ENGAGE AF-TIMI 48)	Not reported (ROCKET-AF)
Long term safety	Not known (study follow up period 1.8 years)	Not known (study follow up period 2 years)	Not known (study median follow up period 2.5 years)	Not known (study follow up period 1.9years)
Missed dose/ dosing errors for NVAF indication	If a dose is missed and there is more than six hours to your next dose, take the missed dose immediately. Take the next scheduled dose as normal If a dose is missed and there is less than	If a dose is missed and there is more than six hours to your next dose, take the missed dose immediately. Take the next scheduled dose as normal. If a dose is missed and there is less than	If a dose is missed, the dose should be taken immediately and then be continued the following day with the once-daily intake as recommended. **The dose should not be doubled within**	If a dose is missed and there is more than twelve hours to the next dose, the missed dose should be taken immediately. Take the next scheduled dose as normal.

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	six hours to your next dose, skip the dose you missed and then continue with twice daily intake as before. **The dose should not be doubled within the same day to make up for a missed dose.**	six hours to your next dose, skip the dose you missed and then continue with twice daily intake as before. **The dose should not be doubled within the same day to make up for a missed dose.**	**the same day to make up for a missed dose.**	If there is less than twelve hours to the next dose, skip the dose that was missed and take the next scheduled dose as normal. **The dose should not be doubled within the same day to make up for a missed dose.**
Reversibility	Andexanet alfa (Ondexxya® ▼) NICE only recommends andexanet alfa (TA697) as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if the bleed is in the gastrointestinal tract, Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage; ICH), in the form of an ongoing randomised trial mandated by the regulator.	Idarucizumab (Praxbind®)	No licensed medicine, clinical trials ongoing. Refer to edoxaban SPC section 4.9, for management of bleeding.	Andexanet alfa (Ondexxya® ▼) NICE only recommends andexanet alfa (TA697) as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if the bleed is in the gastrointestinal tract, Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage; ICH), in the form of an ongoing randomised trial mandated by the regulator.
Half-life	12 hours	GFR ≥ 80 approx. 13 hrs GFR ≥ 50-< 80 approx. 15 hrs GFR ≥ 30-< 50 approx. 18 hrs	10-14 hours	5-9 hours in young individuals 11-13 hours in the elderly
Use in elderly	Non-valvular AF (NVAF): No dose adjustment required unless criteria for reduction met. Increasing age may increase haemorrhagic risk. There is also a risk of increased bleeding when used alongside aspirin in elderly patients.	Dose reduction recommended Patients aged ≥80 years: daily dose of 220 mg dabigatran etexilate taken as one 110 mg capsule twice daily dose reduction for consideration Patients between 75-80 years: daily dose of dabigatran etexilate of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of	After taking renal function and body weight into account, age had no additional clinically significant effect on edoxaban pharmacokinetics in a population pharmacokinetic analysis of the pivotal Phase 3 study in NVAF (ENGAGE AF-TIMI 48). No dose reduction is required, though coadministration with aspirin is	Increasing age may increase haemorrhagic risk. No dose adjustment is required.

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		bleeding. The effect by age on exposure to dabigatran was confirmed in the RE-LY study with an about 31% higher trough concentration for subjects ≥75 years and by about 22% lower trough level for subjects <65 years compared to subjects between 65 and 75 years.	cautioned due to higher bleed risk.	
Gender	No dose adjustment required.	No dose adjustment required.	No dose adjustment required.	No dose adjustment required.
Ethnicity	No dose adjustment required.	No dose adjustment required.	No dose adjustment required.	No dose adjustment required.
Pregnancy and breastfeeding- refer to specialist anticoagulation services	Not recommended during pregnancy. A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy.	Should not be used during pregnancy unless clearly necessary. Breast-feeding should be discontinued during treatment.	Contraindicated in pregnancy and breast feeding.	Contraindicated in pregnancy and breast feeding.
Fertility	Studies in animals dosed with apixaban have shown no effect on fertility.	No human data available. See SPC for animal data.	No specific studies with edoxaban in human beings have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen.	No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen.
Extremes of weight (General)	The relative dose of DOACs may vary by 20–30% at extremes of bodyweight (< 50–60 kg or > 100–120 kg). This may be problematic given the difficulties in monitoring the therapeutic effects. Guidelines from the International Society on Thrombosis and Haemostasis (ISTH) recommend not using a DOAC in people greater than 120 kg or with a BMI greater than 40 due to limited clinical data available for this patient group. However, the ISTH guidelines recommend that if a DOAC is to be commenced in a person who is greater than 120 kg or has a BMI greater than 40 then drug-specific peak and trough level should be measured. This may require specialist input. If the level falls within the expected range, consensus opinion from the international guidelines is to continue the DOAC. In 2021, the ISTH guidelines recommend not to regularly measure peak or trough drug specific DOAC levels. However, the updated recommendations relate to DOAC use for the treatment and prevention of venous thromboembolism. Anticoagulation (warfarin or DOAC) in patients less than 50 kg should be used with caution.			

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Extremes of weight	NVAF: No dose adjustment required unless criteria for reduction met. Low body weight (<60kg) may increase haemorrhagic risk.	No dose adjustment necessarily, but close clinical surveillance is recommended in patients with a body weight <50kg.	Dose adjustment suggested (to **30mg once daily**) in those **≤ 60 kg**.	In adults, extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary.
Renal impairment	Renal function should be assessed prior to DOAC treatment in all patients. Creatinine clearance must be calculated, eGFR is NOT considered a suitable alternative. Consider agents which are less dependent on the kidney for excretion. Renal clearance for each DOAC (expressed as a percentage of clearance of total absorbed dose) is: apixaban (27%), rivaroxaban (35%), edoxaban (50%), dabigatran etexilate (80%). Edoxaban is associated with decreasing efficacy with increasing creatinine clearance. The SPC advises edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk. SPS suggest consider using another anticoagulant if CrCL >95ml/min.			
CrCl >50mL/min	May need dose reduced to 2.5mg twice daily (dependent on age and body weight).	No adjustment required.	Use as for normal renal function (60mg once daily).	No adjustment required.
CrCl 30-49mL/min	May need dose reduced to 2.5mg twice daily (dependent on age and body weight).	For patients with high risk of bleeding, a dose reduction of dabigatran etexilate to 220 mg taken as one 110 mg capsule twice daily should be considered. Close clinical surveillance is recommended in patients with renal impairment.	Dose recommendation of 30mg once daily.	The recommended dose is 15mg once daily.
CrCl 15-29mL/min	Use lower dose of 2.5mg twice daily	Contraindicated.	Dose recommendation of 30mg once daily.	Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, rivaroxaban is to be used with caution in these patients. The recommended dose is 15mg once daily.
CrCl <15mL/min	Not recommended	Contraindicated.	Not recommended.	Not recommended
Administration	Apixaban should be taken with water, with or without food.	Dabigatran can be taken with or without food. Capsules should be swallowed whole	Edoxaban can be taken with or without food.	Doses of 20mg or 15mg tablets must be taken with food. If taken on an empty stomach, oral bioavailability of 20mg

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		with a glass of water (to facilitate delivery to the stomach). Capsules should not be opened as this may increase the risk of bleeding.		and 15mg may be reduced by a third.
Swallowing difficulties	Tablets can be crushed and mixed in water, 5% dextrose in water or apple juice / apple puree and are stable for up to 4 hours. **Licensed administration.**	Capsules should not be opened. Consider alternative anticoagulant in patients with swallowing difficulties. **Unlicensed administration.**	Tablets can be crushed and mixed with water or apple puree. Administer immediately **Licensed administration.**	Tablets can be crushed and mixed with water or apple puree. Crushed tablets should be immediately followed by food. **Licensed administration.**
Lactose & wheat Content	Contain lactose No wheat	No lactose or wheat	No lactose or wheat	Contains lactose No wheat
Food interactions	No specific foods known to interact – see administration section above for advice on taking with or without food			
Compliance aids	The manufacturer does not or cannot recommend use in a compliance aid but there are no theoretical concerns.	Not suitable for a compliance aid; theoretical risk that the preparation is very sensitive to moisture. Dabigatran should be left in individual foil wrapping until administration. Individual foil blisters should not be placed in a compliance aids there are case reports of patients swallowing the foil blister and causing injuries.	Use in compliance aids has not been studied.	The manufacturer does not or cannot recommend use in a compliance aid but there are no theoretical concerns.
Storage requirements	No special storage requirements.	Store in original package to protect from moisture.	No special storage requirements.	No special storage requirements.
Cardioversion (NVAF)	Apixaban can be initiated or continued in NVAF patients who may require cardioversion. See the SPC for full details on use.	Patients can stay on dabigatran etexilate while being cardioverted.	Edoxaban can be initiated or continued in patients who may require cardioversion. See SPC for details	Rivaroxaban can be initiated or continued in patients who may require cardioversion. See SPC for details
Conversion from warfarin to DOAC	Discontinue warfarin and start apixaban when the INR < 2.0.	Discontinue warfarin and start dabigatran when INR < 2.0.	Discontinue warfarin and start edoxaban when the INR < 2.5.	Discontinue warfarin and start rivaroxaban when INR ≤ 3.0 for prevention of stroke and systemic embolism.
Conversion from DOAC to warfarin (Administration of DOACs can impact INR values. Until DOAC is	Give warfarin and apixaban concurrently until the INR is ≥ 2.0. Initiate warfarin at standard dose for 2 days and then dose as per INR. Obtain an INR prior to the next scheduled dose of apixaban.	Adjust the starting time of warfarin based on CrCl as follows: • CrCl ≥ 50 mL/min, start warfarin 3 days before discontinuing dabigatran. • CrCl ≥ 30-49 mL/min, start	There is a potential for inadequate anticoagulation during the transition from edoxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. Patients should	Give warfarin and rivaroxaban concurrently until the INR is ≥ 2.0. Initiate warfarin at standard dose for 2 days and then dose as per INR. INRs should be taken at least 24hrs after the previous dose of rivaroxaban

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stopped interpret these with caution. INRs should be taken immediately before the next DOAC dose.)		warfarin 2 days before discontinuing dabigatran INRs may be falsely elevated until dabigatran has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.	not take a loading dose of warfarin in order to promptly achieve a stable INR. It is recommended that during the first 14 days of concomitant therapy the INR is measured at least three times just prior to taking the daily dose of edoxaban to minimise the influence of edoxaban on INR measurements. **Oral option:** For patients taking: • 60 mg of edoxaban, reduce the dose to 30 mg and begin warfarin concomitantly. • 30 mg of edoxaban, reduce the dose to 15 mg and begin warfarin concomitantly. INR must be measured at least weekly and just prior to the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR ≥ 2.0 is achieved, edoxaban should be discontinued and the warfarin continued. **Parenteral option:** Discontinue edoxaban and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR ≥ 2.0 is achieved the parenteral anticoagulant should be discontinued and the warfarin continued.	(immediately before the) next dose. INRs may be falsely elevated during rivaroxaban therapy, but once rivaroxaban is discontinued, may be done reliably at least 24 hours after the last dose.
Conversion from parenteral anticoagulants to DOAC These medicinal products should not be	Give the first dose of apixaban at the time the next parenteral anticoagulant dose is due.	The parenteral anticoagulant should be discontinued and dabigatran etexilate should be started 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g., intravenous	**Subcutaneous anticoagulant (i.e. low molecular weight heparin (LMWH), fondaparinux):** Discontinue subcutaneous anticoagulant and start edoxaban at the time of the next scheduled subcutaneous anticoagulant dose.	**LMWH:** Discontinue LMWH and start rivaroxaban 0 to 2 hours before the time of the next scheduled dose. **UFH:** Start rivaroxaban at the time of discontinuation of UFH.

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administered simultaneously.		Unfractionated Heparin (UFH)).	**Intravenous unfractionated heparin (UFH):** Discontinue the infusion and start edoxaban 4 hours later.	
Conversion from DOAC to parenteral anticoagulant These medicinal products should not be administered simultaneously.	Discontinue apixaban and give the first dose of parenteral anticoagulant at the time the next apixaban dose would be taken.	Discontinue dabigatran and wait 12 hours after the last dose of dabigatran before switching to a parenteral anticoagulant.	Discontinue edoxaban and start the parenteral anticoagulant at the time of the next dose of edoxaban.	Discontinue rivaroxaban and give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken.
Switching from DOAC to DOAC *In patients with renal impairment, higher than therapeutic plasma concentrations are expected and a longer interval may be required.	Discontinue current DOAC and start alternative DOAC at the time that the next scheduled dose would be due. Patients must not be on more than one drug at once.	Discontinue current DOAC and start alternative DOAC at the time that the next scheduled dose would be due. Patients must not be on more than one drug at once.	Discontinue current DOAC and start alternative DOAC at the time that the next scheduled dose would be due. Patients must not be on more than one drug at once.	Discontinue current DOAC and start alternative DOAC at the time that the next scheduled dose would be due. Patients must not be on more than one drug at once.
Hepatic impairment	**LFTs should be checked prior to initiation.** Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in patients with severe hepatic impairment. Use with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B), but no dose adjustment is required. Caution in patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥1.5 x ULN as these patients were excluded in clinical trials.	**LFTs should be checked prior to initiation.** Contraindicated in hepatic impairment or liver disease expected to have any impact on survival. Not recommended in mild- moderate hepatic impairment with liver enzymes >2 ULN.	**LFTs should be checked prior to initiation.** Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in patients with severe hepatic impairment. Use with caution in patients with mild- moderate hepatic impairment with liver enzymes >2 ULN or total bilirubin >1.5ULN.	**LFTs should be checked prior to initiation.** Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (moderate and severe).

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Summary of drug interactions (List not exhaustive– refer to current SPC www.medicines.org.uk)	Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole and posaconazole. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort, erythromycin, and clarithromycin.	Avoid with HIV protease inhibitors, rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort, dronedarone, ciclosporin, tacrolimus, ketoconazole, itraconazole, voriconazole and posaconazole. Caution with amiodarone, verapamil, erythromycin, and clarithromycin.	No data on co-administration with HIV protease inhibitors. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort, and clarithromycin. Dose reduce with ciclosporin, dronedarone, erythromycin or ketoconazole.	Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole, posaconazole and dronedarone. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's wort, erythromycin, and clarithromycin.
Specific Drug Interactions				
HIV protease inhibitors	Avoid	Avoid	No data	Avoid
Antiarrhythmics				
Amiodarone *N.B. Amiodarone has a long half-life and so interaction risk may persist for some time after discontinuation*	Caution - may increase plasma levels of apixaban but dose adjustment is not required.	Caution - may increase plasma levels of dabigatran.	Caution - may increase plasma levels of edoxaban but dose adjustment is not required.	No current data available.
Dronedarone	Caution – may increase plasma levels of apixaban.	Contra-indicated.	Requires dose reduction to 30 mg once daily.	Combination has been proven to be clinically unsafe and should be avoided.
Quinidine	Quinidine is expected to increase apixaban levels, but dose adjustment is not required.	Caution – may increase plasma levels of dabigatran.	Caution – may increase plasma levels of edoxaban but dose adjustment is not required.	No current data available
Digoxin	No dose adjustment necessary. Levels of digoxin appear to be unaffected by apixaban.	No dose adjustment necessary. Levels of digoxin appear to be unaffected by dabigatran.	No adjustment necessary, though levels of both digoxin and edoxaban appear to increase.	No adjustment necessary, though levels of both digoxin and edoxaban appear to increase.
Antiepileptics				
Carbamazepine	Carbamazepine, phenobarbital, and phenytoin are a strong inducers of both CYP3A4 and P-gp. Concommitant use does not require apixaban dose adjustment, but caution is required.	Avoid - carbamazepine is an inducer of P-gp, of which dabigatran is a substrate and concurrent use is expected to result in decreased dabigatran concentrations.	Caution - carbamazepine is an inducer of P-gp, of which edoxaban is a substrate and concurrent use is expected to result in decreased edoxaban concentrations.	Avoid, unless able to monitor closely for signs and symptoms of thrombosis. Carbamazepine, phenobarbital, and phenytoin are strong inducers of CYP3A4. In clinical trials, rifampicin (another strong inducer of CYP3A4) significantly decreased pharmacodynamics effects of rivaroxaban.
Phenobarbital		No current data available.	Use with caution. Phenobarbital is an inducer of P-gp, of which edoxaban is a substrate and concurrent use is expected to result in decreased edoxaban concentrations.	

	Apixaban	Dabigatran etexilate (as mesilate)	Edoxaban	Rivaroxaban ▼
Phenytoin		Avoid - phenytoin is an inducer of P-gp, of which dabigatran is a substrate and concurrent use is expected to result in decreased dabigatran concentrations.	Caution - phenytoin is an inducer of P-gp, of which edoxaban is a substrate and concurrent use is expected to result in decreased edoxaban concentrations.	
Azole antifungals *Ketoconazole, Itraconazole, Voriconazole, Posaconazole*	Avoid - these azole antimycotics are strong inhibitors of both CYP3A4 and P-gp, and co-administration with apixaban is associated with a significant rise in apixaban levels.	Avoid - combination has been proven to be clinically unsafe or no data available. (Ketoconazole = contra-indicated)	Ketoconazole: concurrent use requires edoxaban dose reduction to 30mg once daily as ketoconazole increases edoxaban plasma levels. Posaconazole and voriconazole: no current data available. Itraconazole: caution – may increase plasma levels of edoxaban.	Avoid - concurrent use with these agents is not recommended due to known interaction with ketoconazole. All of these medicines are strong inhibitors of both CYP3A4 and P-gp.
Fluconazole	Fluconazole is expected to increase apixaban levels, but dose adjustment is not required.	No current data available.	No current data available.	Concurrent use is cautioned but dose adjustment not necessary.
Clarithromycin / Erythromycin	Caution – may slightly increase plasma levels of apixaban but dose adjustment is not required.	Caution – may increase plasma levels of dabigatran.	Erythromycin – reduce edoxaban dose to 30mg once daily. Clarithromycin – caution may increase plasma levels of edoxaban	Caution- particularly in renal impairment. Erythromycin may interact with rivaroxaban and increase the risk of bleeding – consider this interaction when prescribing antibiotics and follow precautions in the product information if concomitant use is necessary (Dec 20 MHRA drug safety update).
Rifampicin	Caution - rifampicin is a strong inducer of both CYP3A4 and P-gp but concomitant use does not require apixaban dose adjustment for use in NVAF.	Avoid - rifampicin is a strong inducer of P-gp, of which dabigatran is a substrate. Concurrent use is expected to result in decreased dabigatran concentrations.	Avoid – rifampicin is a P-gp inducer rifampicin and concomitant use could lead to a decrease in mean edoxaban AUC and a shortened half-life, with possible decreases in its pharmacodynamic effects.	Avoid, unless able to monitor closely for signs and symptoms of thrombosis. Rifampicin (a strong inducer of CYP3A4) significantly decreases the pharmacodynamics effects of rivaroxaban.
Calcium channel blockers, non-dihydropyridine *Diltiazem Verapamil*	Non-dihydropyridine calcium channel blockers (diltiazem, verapamil) are expected to increase apixaban levels, but dose adjustment is not required.	Caution – verapamil may increase plasma levels of dabigatran (max dabigatran dose 110mg twice daily taken at the same time as verapamil). No dose adjustment required when used with diltiazem.	Caution - whilst verapamil is expected to affect P-gp efflux of edoxaban, dose reduction is not required based on clinical data.	Caution (particularly in those with renal impairment) - verapamil slightly increases the exposure to edoxaban and rivaroxaban. Diltiazem might similarly interact with rivaroxaban.

	Apixaban	Dabigatran etexilate (as mesilate)	Edoxaban	Rivaroxaban ▼
Non-steroidal anti-inflammatory drugs (NSAIDs) *Naproxen*	Caution – increased bleeding risk.	NSAIDs given for short-term analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50% on both dabigatran etexilate and warfarin.	Chronic use of NSAIDs with edoxaban is not recommended.	Caution – increased bleeding risk.
Oral contraceptives	No current data available.	No current data available.	No current data available.	No current data available.
Hormone Replacement Therapy	No current data available.	No current data available.	No current data available.	No current data available.
SSRIs	Use with caution with as SSRIs increase the risk of bleeding.	Use with caution with as SSRIs increase the risk of bleeding.	Use with caution with as SSRIs increase the risk of bleeding.	Use with caution with as SSRIs increase the risk of bleeding.
SNRIs	Use with caution with as SNRIs increase the risk of bleeding.	Use with caution with as SNRIs increase the risk of bleeding.	Use with caution with as SNRIs increase the risk of bleeding.	Use with caution with as SNRIs increase the risk of bleeding.
St. John's Wort	Caution – may lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required.	Avoid - St. John's Wort is an inducer of P-gp, of which dabigatran is a substrate and concurrent use is expected to result in decreased dabigatran concentrations.	Caution - St. John's Wort is an inducer of P-gp, of which edoxaban is a substrate and concurrent use is expected to result in decreased edoxaban concentrations.	Avoid - the concomitant use of rivaroxaban with other strong CYP3A4 inducers may lead to reduced rivaroxaban plasma concentrations.
Platelet aggregation inhibitors and NSAIDs including Acetylsalicylic acid (ASA) and platelet aggregation inhibitors	Care is to be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), including ASA and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered. Combination therapy with oral anticoagulants and anti-platelets in patients with AF/IHD/PCI must be decided / initiated on a case-by-case basis by a cardiologist and the duration of the regime clearly documented.			
Anticoagulants Unfractionated heparins, LMWH, heparin derivatives *(e.g. Fondaparinux)* ***Oral anticoagulants*** *(e.g. warfarin)*	Concomitant use of a DOAC with any other anticoagulant agent is contraindicated, except under the circumstances of switching therapy to or from a DOAC or when unfractionated heparin is given at doses necessary to maintain a patent central venous or arterial catheter.			

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Tacrolimus	No current data available.	Use not recommended. Tacrolimus has been found in vitro to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and cyclosporine. Dabigatran etexilate has not been clinically studied together with tacrolimus.	Caution – may increase plasma levels of edoxaban.	No current data available.
Ciclosporin	Caution – predicted to increase exposure to apixaban.	Contraindicated	Reduce edoxaban dose to 30mg once daily.	Caution – predicted to increase exposure to rivaroxaban.

USEFUL LINKS

Specialist Pharmacy Service

- Is it safe to take herbal medicines with non-vitamin K antagonist oral anticoagulants (NOACs)?
- Can small volume intramuscular injections be given to patients taking oral anticoagulants?
- Using oral anticoagulants in breastfeeding women
- Direct Acting Oral Anticoagulants (DOACs) in Renal Impairment: Practice Guide To Dosing Issues
- Non-vitamin K antagonist oral anticoagulants (NOACs): Is it safe to take them with herbal medicines?

NICE

- NICE guideline [NG196]: Atrial fibrillation: diagnosis and management

European Society of Cardiology

- ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS
- Novel Oral Anticoagulants for Atrial Fibrillation

MHRA Drug Safety Updates

- Direct-acting oral anticoagulants (DOACs): reminder of bleeding risk, including availability of reversal agents
- Erythromycin: caution required due to cardiac risks (QT interval prolongation); drug interaction with rivaroxaban
- Rivaroxaban (Xarelto▼): reminder that 15 mg and 20 mg tablets should be taken with food
- Direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome
- Prescribing medicines in renal impairment: using the appropriate estimate of renal function to avoid the risk of adverse drug reactions
- Rivaroxaban (Xarelto▼) after transcatheter aortic valve replacement: increase in all-cause mortality, thromboembolic and bleeding events in a clinical trial
- New oral anticoagulants apixaban (Eliquis▼), dabigatran (Pradaxa) and rivaroxaban (Xarelto▼) Risk of serious haemorrhage—clarified contraindications apply to all 3 medicines
- Direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome
- Dabigatran (Pradaxa▼): risk of serious haemorrhage
- Dabigatran (Pradaxa): contraindicated in patients with prosthetic heart valve(s) requiring anti-coagulant treatment

UKCPA

- The Handbook of Perioperative Medicines – Direct Oral Anticoagulants

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