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BERKSHIRE WEST APC

NOAC use in atrial fibrillation

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Adapted from Buckinghamshire CCG guidance

This guideline provides prescribing and monitoring guidance for anticoagulation with new oral anticoagulants (NOACs) in AF treatment for adults and should be read in conjunction with the Summary of Product Characteristics (SPC) available on http://www.medicines.org.uk/emc and the BNF.

DABIGATRAN, RIVAROXABAN, EDOXABAN AND APIXABAN FOR ATRIAL FIBRILLATION (AF)
Initiation guideline

1. SUMMARY

1.1 AF is a condition which results in an increased risk of stroke. Warfarin has always been the main anticoagulant used in the UK for primary and secondary prevention of stroke in patients with AF and remains a very effective treatment for patients.

1.2 Dabigatran, rivaroxaban apixaban and edoxaban have also been approved by NICE for this indication. These new oral anticoagulants (NOACs) are unlike warfarin as they are not vitamin K antagonists and do not require regular INR monitoring however renal function should be regularly monitored.

1.3 Each of the NOACs has a different side effect profile.

1.4 At present, only dabigatran has a licensed antidote.

1.5 All anticoagulants, whether vitamin K antagonists or NOAC, are associated with serious bleeding risks and require careful risk assessment of the patient prior to initiation.

1.6 The decision about whether to start treatment with a NOAC should be made after an informed discussion between the clinician and the patient about the risks and benefits of NOACs compared with warfarin. For patients who are taking warfarin, the potential risks and benefits of switching to a NOAC should be considered in light of their level of INR control.

1.7 The risk assessment, informed discussion and decision about choice of anticoagulant will be performed between the patient and GP.

1.8 Those patients started on a NOAC should be reviewed at 2 weeks before ongoing prescribing and monitoring to identify any significant concerns or toxicities.

1.10 If side effects or concerns, make a further review of anticoagulation options. At this point, anticoagulation should be stopped and an alternative anticoagulant is prescribed.

2. BACKGROUND FOR USE

2.1 Anticoagulation is recommended in patients with AF with a CHA2DS2VASc ≥1 for men or ≥2 for women. Where a patient presents with a TIA or stroke, in the absence of alternative causes and where paroxysmal AF cannot be ruled out, anticoagulation is considered.

2.2 Warfarin has been used for over 60 years for anticoagulation and is monitored using INR allowing individualised dosing and reinforcement of compliance. The practicalities of monitoring and adherence with complex dosage regimens, especially for patients with multiple co-morbidities, makes warfarin challenging for some patients. Thus many patients who could benefit from anticoagulation do not receive it.

2.3 In line with NICE Guidelines for the NOACs they may be considered as alternatives to warfarin in patients with AF, in whom oral anticoagulation is indicated CHA2DS2VASc ≥1 for men or ≥2 for women.

2.4 NOACs do not require INR monitoring. **The reduced monitoring and dosage adjustment requirements need to be weighed against the lack of long term safety data, antidote, and limited data at extremes of age, weight, renal function or liver function.**

2.5 All anticoagulants can cause significant bleeding risk. Before starting any anticoagulant careful consideration of bleeding risk should be undertaken. Tools such as the HASBLED score should be used to help quantify the bleeding risk

2.6 The CHA2DS2VASc and HASBLED scores share risk factors and as a result, patients at high risk of stroke (high CHA2DS2VASc score) often also have a high HASBLED score. Steps should be taken to reduce the bleeding risk through a reduction in modifiable risk factors for bleeding such as uncontrolled BP.

3. CRITERIA FOR USE

Warfarin remains the first line option for initiation of anticoagulation unless the criteria below are met.

3.1 NEW patients generally suitable to start NOAC

3.1.1 High risk of interactions with warfarin leading to unacceptable INR fluctuations which cannot be addressed.

3.1.2 Co-morbidities which make INR control challenging (clinically unstable or medically complex), e.g. unstable severe COPD, uncontrolled LVF, recurrent cellulitis.

3.1.3 Adherence to variable dosage regimens is likely to be poor, e.g. learning disabilities.

3.1.4 Secondary prevention of AF patients with recent stroke or TIA to be initiated by a consultant in the secondary care stroke service. This is initiated at least 2 weeks after the stroke or TIA when there has been associated brain infarction.

3.2 EXISTING WARFARIN PATIENTS generally NOT suitable to start NOAC (to remain on warfarin)

3.2.1 Good INR control assessed by Time in Therapeutic Range (TTR)>70% - patients should be advised that there is no clear data to support switching to NOAC in patients with good INR control. There are clear disadvantages/risks associated with NOAC as described above.

3.2.2 Patients taking warfarin for indications other than anticoagulation in non-valvular AF, unless licensed in these groups.

3.2.3 Patients with mitral valve disease or mechanical heart valve replacements (unlicensed in this group even if the patient has co-existing AF).

3.3 EXISTING patients who may be suitable to consider a NOAC or warfarin

3.3.1 Moderate INR control (TTR 60 to 69%) despite evidence of compliance – patients should be advised that the benefit from switching to a NOAC is unclear. Efforts should be made to find and resolve underlying causes of reduced control. If this improves impossible then a switch to a NOAC may be considered but NOAC disadvantages/risks as described above should first be discussed.

3.4 EXISTING patients generally suitable to start NOAC

3.4.1 Poor INR control (TTR <60%), despite evidence of compliance and adequate vitamin K intake.

3.4.2 Allergy to or intolerable side effects from warfarin which would require warfarin withdrawal.

4. TABLE OF CONSIDERATIONS WHEN DECIDING WHICH NOAC FOR AF

General principle: When all considerations are equal, priority will be given to the product with the greatest experience of use and lowest long term costs.

Characteristic	Drug choice	Rationale
Mechanical valve or valvular AF	NOACs contraindicated	NOACs effectively contraindicated. Recent REALIGN phase lll dose ranging study of dabigatran in patients with mechanical valves was terminated early due to an increase in adverse events including stroke, MI, bleeding and valve thrombosis.
Severe renal impairment (CrCl <30 ml/min)	NOACs not recommended See section 5.1.8	Dabigatran contraindicated. Apixaban, Rivaroxaban and edoxaban – lower doses have been approved for patients with CrCl 15 - 30 ml/min, however these are largely based on pharmacokinetic data, rather than clinical trial data use with caution.
Moderate renal impairment (CrCl 30 - 50 ml/min)	Rivaroxaban or apixaban or edoxaban	Factor Xa inhibitors less affected by impaired renal function than dabigatran (renal excretion 80% for dabigatran, 50% for edoxaban, 33% for rivaroxaban and 25% for apixaban).
Increased risk of GI bleed	Apixaban	Higher rates of GI bleeding with dabigatran, rivaroxaban and edoxaban compared to warfarin. Apixaban only agent to show a reduction in GI bleeding in addition to an overall reduction in bleeding rates when compared with warfarin.
Mucous membrane bleeding (includes nosebleeds, haematuria, vaginal bleeding)	Dabigatran	Mucous membrane bleeding is more common with antiXas (apixaban, edoxaban and rivaroxaban) compared with warfarin. Mucous membrane bleeding risk is similar with dabigatran and warfarin.
Recent ischaemic stroke on warfarin	Dabigatran	Dabigatran (at a dose of 150 mg bd) is the only NOAC shown to be superior to warfarin in reducing ischaemic stroke.
Recent ACS	Rivaroxaban	Small increase in MI with dabigatran (although subsequent analysis has suggested this apparent increase is not statistically significant). Rivaroxaban has demonstrated benefit in patients with recent ACS (ATLAS ACS 2TIMI 51 trial). Apixaban has demonstrated neither benefit nor harm.
Moderate or severe heart failure	Dabigatran	Peripheral oedema can occur with Rivaroxaban, apixaban and edoxaban.
Concurrent treatment of DVT and/or PE or prevention of recurrent DVT and/or PE	Rivaroxaban or Apixaban	See VTE policy
Poor compliance with twice daily dosing	Rivaroxaban or edoxaban	Only NOACs that are once daily administration.
Patient requiring a compliance aid, e.g. dosette box	Rivaroxaban or Apixaban or edoxaban	Dabigatran not stable in a compliance aid.
Administration via enteral feeding tube	Rivaroxaban or apixaban	Dabigatran capsules need to be swallowed whole. Opening the capsules results in a significant increase in bioavailability

5. CONTRAINDICATIONS AND PRECAUTIONS

All clinical contraindications to warfarin anticoagulation are also contraindications to NOACs.

5.1 Absolute contraindications to warfarin and NOACs

5.1.1 Known large oesophageal varices.

5.1.2 Significant thrombocytopenia (platelet count <50 x 109/L) - *refer to haematologist.*

5.1.3 Within 72 hours of major surgery with risk of severe bleeding - *defer and reassess risk post-operatively.*

5.1.4 Previously documented hypersensitivity to either the drug or excipients – *consider cardiology opinion.*

5.1.5 Acute clinically significant bleed - *defer and reassess stroke versus bleeding risk within 3 months.*

5.1.6 Decompensated liver disease or deranged baseline clotting screen (INR ≥1.5) – *refer to Gastroenterology/Hepatology.* ***Contraindication applies to oral anticoagulants only.***

5.1.7 Pregnancy or within 48 hours postpartum - *seek urgent haematological advice.*

Contraindication applies to oral anticoagulants only.

5.1.8 Severe renal impairment. ***Contraindication applies to dabigatran with*** **CrCl <30 mL/min** ***and to apixaban, rivaroxaban and edoxaban with CrCl <15 ml/min***

5.2 Relative contraindications to both warfarin and NOACs

5.2.1. Previous history intracranial haemorrhage - *some AF patients especially those considered at higher stroke risk (i.e. CHADS2 score ≥3) may benefit from antithrombotic therapy, seek the opinion of a stroke specialist.*

5.2.2 Recent major extracranial bleed within the last 6 months where the cause has not been identified or treated *–decision for oral antithrombotic therapy should be deferred.*

5.2.3 Recent documented peptic ulcer (PU) within last 3 months– *decision for oral antithrombotic therapy should be deferred until treatment for PU completed. In all cases with history of PU, give PPI cover whilst on antithrombotic.*

5.2.4 Recent history recurrent iatrogenic falls in patient at higher bleeding risk.

A patient at higher bleeding risk is assessed by having 3 or more of the following risk factors:
– age >65 years
– previous history bleed or predisposition to bleeding (e.g. diverticulitis)
– uncontrolled hypertension
– severe renal impairment (i.e. serum creatinine >200 micromol/L, GFR <30 mL/min/1.73 m2 or on dialysis)
– acute hepatic impairment (e.g. bilirubin >2 x ULN + LFTS >3 x ULN), chronic liver disease (e.g. cirrhosis)
– low platelet count <80 x 109/L or a thrombocytopenia or anaemia of undiagnosed cause
– on concomitant drugs associated with an increased bleeding risk, e.g. SSRIs, oral steroids, NSAIDs, methotrexate or other immune-suppressant agents.

N.B. ***A risk of falls is not a contraindication to initiating oral anticoagulation*** *(e.g. a patient with an annual stroke risk of 5% (CHADS2 score 2 - 3) would need to fall 295 times for fall risk to outweigh stroke reduction benefit of warfarin).*

5.2.5 Dementia or marked cognitive impairment with poor medicines compliance and no access to carer support.

5.2.6 Chronic alcohol abuse – especially if associated with binge drinking.

5.3 Contraindications for NOACs but not for warfarin

5.3.1 Severe renal impairment (CrCl <30 ml/min for dabigatran; CrCl <15 ml/min for rivaroxaban or apixaban).

5.3.2 Hepatic impairment (elevated ALT >2 x ULN) for dabigatran or edoxaban. Liver disease resulting in a coagulopathy or expected to have any impact on survival for any NOAC.

6. RESPONSIBILITIES

6.1 GP responsibilities

6.1.1 To confirm a diagnosis of AF and anticoagulation indicated. The GP should assess the patient using the locally agreed criteria (above). It is not recommended to switch to a NOAC in patients who are well controlled on warfarin

6.1.2 To check or confirm anticoagulation is not contraindicated, including review of BP, U&Es, FBC, LFTs, baseline INR and weight (within the last 3 months). FBC within the last 12months and LFTs and INR if there is any reason to suspect it is abnormal

6.1.3 To decide/confirm benefits of anticoagulation outweigh risks and agree the need for anticoagulation.

6.1.4 To decide on the most appropriate anticoagulant, if any, and initiate treatment following an informed discussion with the person/carer about the risks and benefits of NOAC compared with warfarin, as per local criteria for NOAC use. Where an informed discussion is not possible due to the patient's medical condition, the decision will be made as considered in the best interests of the patient. This initiation may be undertaken by the secondary care stroke service for secondary prevention of stroke or TIA.

6.1.5 To counsel patients or their carer wherever possible.

6.1.6 Patients with insufficient TTR on warfarin will have the reasons explored and addressed wherever possible. If these cannot be resolved then NOAC will be initiated.

6.1.7 To refer those patients initiated on warfarin to their usual anticoagulation service for ongoing monitoring and dosage adjustment.

6.1.8 To contact patients or their carers two to three weeks following initiation of a NOAC to assess the tolerability of the drug and to review if any problems have occurred which can be rectified.

6.1.9 To report serious adverse effects to the MHRA/CHM for dabigatran and all side effects for black triangle NOACs (rivaroxaban, apixaban and edoxaban).

6.2 Patient/carer's responsibilities

6.2.1 To attend all appointments with the patient's GP.

6.2.2 To report any adverse effects to their GP whilst under treatment.

6.2.3 To share any concerns they have in relation to treatment.

6.2.4 Ask the GP if they do not have a clear understanding of their treatment.

7. PRE-TREATMENT ASSESSMENT BY GP

7.1 U&Es and weight within the last 3 months, (to allow CrCl to be calculated) - see appendix A (page 17). **GPs MUST CALCULATE THIS BEFORE INITIATING A NOAC.**

7.2 FBC within last 12 months but recent results are required for patients who have been acutely unwell.

7.3 If previous history suggests any likelihood of abnormal LFTs and/or INR these should also be checked and documented.

8. ONGOING MONITORING SCHEDULE BY GP

8.1 If a switch to warfarin or an alternative NOAC is considered necessary, the patient will need to be referred into the usual anticoagulant pathway on switching from NOAC to warfarin.

8.2 Rivaroxaban, apixaban and edoxaban are monitored intensively by the MHRA and CHM and all adverse reactions should be reported via the yellow card system. Serious adverse reactions should be reported to the MHRA/CHM for dabigatran.

U&E, including assessment of renal function	Annually. More frequently if patient unwell or declining renal function suspected, e.g. loop diuretic dose needs increasing.
BP	Annually . More frequently if systolic close to or above 160mmHg.
FBC including Hb	Only re-check FBC if anaemia is suspected clinically.
Re-check stroke versus bleeding risk, i.e. CHA2DS2VASc exceeds HAS-BLED score	Annually, but more frequently if clinical status changes.
LFTs	Only re-check if any reason to suspect abnormal. If ALT exceeds 2 x UNL seek advice from NOAC service or haematologist

9. SUPPORTING INFORMATION FOR INDIVIDUAL NOACs

9.1 Dabigatran

9.1.1 Dabigatran dosage

110 mg and 150 mg capsules licensed for stroke prevention in non-valvular AF.

Indication	Dose
Prevention of stroke in patients with non-valvular AF and with a **CHA2DS2VASc** of 1 or more for males. **CHA2DS2VASc** of 2 or more for females.	• 150 mg twice daily is the usual dose, preferably with or after food to minimise gastrointestinal side effects. • Some patients may require a reduced dose of 110 mg twice daily, e.g. if high risk of bleeds, CrCl 30 - 50 ml/minute, over 75 and considered a moderate risk of a bleed, over 80, very low body weight, taking verapamil, concurrent antiplatelet agents - clinical discretion and individual patient factors should be taken into account. • Doses should not be added to monitored dosage systems as it is hygroscopic.

9.1.2 Missed doses

A forgotten dabigatran dose may be taken up to 6 hours after the last scheduled dose. From 6 hours prior to the next scheduled dose onwards, the missed dose should be omitted. No double dose should be taken to make up for missed doses.

9.1.3 Switching from warfarin to dabigatran (usually done in secondary care)

In patients taking warfarin, stop the warfarin then the timing of starting dabigatran depends upon the INR:

Most recent INR (in last month or more recently)	Action
<2	Stop warfarin and start dabigatran the same day
2 - 3	Stop warfarin and start dabigatran the next day
>3	Ensure INR is <3 before starting dabigatran (see above)

9.1.4 Switching from dabigatran to warfarin

9.1.4.1 Warfarin should only be started by an expert in anticoagulation. GPs are expected to refer patients into their usual local anticoagulation pathway.

9.1.4.2 The full effect of warfarin is only seen after at least a few days and up to 10 days. Unless immediate cessation is necessary the following schedule should be followed:

- CrCl ≥50 ml/min, start warfarin 3 days before discontinuing dabigatran etexilate.
- CrCl ≥30 - <50 ml/min, start warfarin 2 days before discontinuing dabigatran etexilate.

9.1.4.3 Because dabigatran can contribute to an elevated INR, INR testing should not be performed until dabigatran has been stopped for at least 2 days.

9.1.5 Dabigatran time to response

Full anticoagulation is expected within 2 hours of initiation.

9.1.6 Dabigatran side effects and actions to be taken (see SPC for full list)

Please report serious suspected side effects through the yellow card system. The following table covers the common side effects listed in the SPC. For uncommon and rare effects - see SPC to determine if they could be due to the drug and seek advice if severe.

Side Effects	Action
Dyspepsia, abdominal pain, nausea and diarrhoea are all common	These side effects may improve over time if the patient persists with treatment. Reinforce need to take with food or a full glass of water. A PPI or H_2 antagonist may need to be initiated or the existing PPI dose may need to be increased. If significant symptoms review choice of anticoagulant.
GI bleeds	Major GI bleed risk was twice as high with dabigatran 150 mg twice daily than with warfarin in RE-LY. The mainstay of treatment is to stop the drug and provide supportive care. Severe bleeds may require hospital admission. Praxbind is the available antidote and can only be used within hospital.
Risk of bleeding	The drug is renally excreted and will accumulate and potentially cause toxicity if prescribed in patients with a CrCl <30 ml/min. Dabigatran is contraindicated if CrCl <30 ml/min - stop the drug and review alternative choices of anticoagulation. An MHRA safety alert (Dec 2011) confirmed dabigatran is associated with increased bleeding risks when given in moderate and severe renal impairment. Interacting drugs may also increase dabigatran levels and risk of a bleeding.
Anaemia	If Hb <80 g/L do not start anticoagulation until anaemia has been treated and resolved. If Hb 80 – 100 g/L review the urgency of anticoagulation and seek advice if there is a need to anticoagulate quickly. If Hb 101 g/Lor more it is safe to anticoagulate, although treatment of any underlying reasons for anaemia is recommended.
Hepatic enzymes elevated	If small increase re-test. If LFTs exceed 2 x ULN stop dabigatran and seek advice.
Nose bleeds	These are common. Check & exclude raised BP as contributory factor In most patients it is safe to continue treatment. If clinically concerned about acute or recurrent epistaxis please seek further advice.
Myocardial infarction or ischaemic heart disease (IHD): There was a statistically insignificant increased number of MIs in the dabigatran arm of RE-LY.	Ideally avoid dabigatran use in patients with a past history if IHD; review benefits versus risks if there is a compelling need to treat, warfarin may be a safer option.

9.1.7 Dabigatran drug interactions (refer to BNF and SPC)

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and have no *in vitro* effects on human cytochrome P450 enzymes. Dabigatran is however a substrate at P-glycoprotein receptors (P-gp) and clinically relevant interactions can occur.

Summary of Drug Interactions for Dabigatran

Class	Drugs	Effect	Action
Strong P-gp inhibitors	Dronedarone Ketoconazole Itraconazole Ciclosporin Tacrolimus Posaconazole	Levels of dabigatran increased by ~150% for ketoconazole and ~100% for dronedarone.	Combination contraindicated.
Other strong P-gp inhibitors	Amiodarone Quinidine Verapamil	Levels of dabigatran increased by ~50 - 60%	Reduce dose to 110 mg bd. Please note that due to the long half-life of amiodarone, the potential for interaction may persist for several weeks after stopping amiodarone. Reduce dose to 110 mg bd, advise patient to take simultaneously, monitor carefully. Largest increase in dabigatran levels observed when verapamil administered one hour prior to dabigatran with no significant increase when administered two hours after dabigatran.
Moderate P-gp inhibitors	Clarithromycin Erythromycin	Levels of dabigatran increased by ~20%	No dose reduction required. Monitor closely. Consider use of azithromycin (safer alternative).
P-gp inducers	Rifampicin Carbamazepine Phenytoin St John's Wort	Levels of dabigatran decreased	Combination contraindicated.
	Aspirin Clopidogrel NSAIDs	Increased risk of bleeding	Combination not recommended. Consider GI protection. Close monitoring for signs of bleeding.
	SSRIs	Increased risk of bleeding	If combination is needed then consider GI protection if not already prescribed.
	Prasugrel Ticagrelor	Increased risk of bleeding	Avoid combination.
	Protease inhibitors, e.g. ritonavir	May increase or decrease risk of bleeding	Avoid combination.

9.2 Rivaroxaban

9.2.1 Dosage

Rivaroxaban is licensed for stroke prevention in non-valvular AF.

Indication	Dose
Prevention of stroke in patients with non-valvular AF and with a CHA2DS2VASc of 1 or more for males. **CHA2DS2VASc** of 2 or more for females.	• Rivaroxaban 20 mg daily is the usual dose • If CrCl 15 – 49 ml/minute 15 mg daily is the recommended dose • The dose is best taken with or after food to increase bioavailability

9.2.1 Rivaroxaban missed doses

A forgotten rivaroxaban dose may be taken as soon as the patient remembers, on the same day. No double dose should be taken to make up for missed doses.

9.2.3 Switching from warfarin/dabigatran to rivaroxaban

This is undertaken with advice from secondary care.

9.2.4 Rivaroxaban time to response

Full anticoagulation is expected within 2 - 4 hours of initiation.

9.2.5 Rivaroxaban side effects and actions to be taken (see SPC for full list)

Rivaroxaban is a new drug and is marked ▼ in the BNF which signifies intensive monitoring by the MHRA. Please report all suspected side effects through the yellow card system. There is a lack of long term follow up data available. The following table covers the common side effects listed in the SPC. For uncommon and rare effects see SPC to determine if they could be due to the drug and seek advice if severe.

Side Effects	Action
Risk of bleeding	Patients who bleed do not respond to vitamin K and so the majority of the management is supportive care - The drug is 33% renally excreted and will accumulate and potentially cause toxicity if prescribed in patients with a severe renal failure. Rivaroxaban is contraindicated if CrCl <15 ml/min - stop the drug and review alternative choices of anticoagulation
Oedema	Review, especially if increasing shortness of breath or oedema.
Anaemia	If Hb <80 g/L do not start anticoagulation until anaemia has been treated and resolved. If Hb 80 – 100 g/L review the urgency of anticoagulation and seek advice if there is a need to anticoagulate quickly. If Hb 101 g/L or more it is safe to anticoagulate, although treatment of any underlying reasons for anaemia is recommended.
Dizziness, headache, syncope	Review anticoagulation options. Severe symptoms can result in falls and inability to drive. Even if mild symptoms, because they do not improve with time, it will affect compliance.
Eye haemorrhage, haematuria, vaginal bleeding	Treat symptomatically, seek expert advice if necessary.
Tachycardia	Unless clinically worrying does not require action.
Dyspepsia, abdominal pain, nausea and diarrhoea are all common	These side effects may improve over time if the patient persists with treatment. Reinforce need to take with food or a full glass of water. A PPI or H_2 antagonist may need to be initiated or the existing PPI dose may need to be increased. If significant symptoms continue, rivaroxaban should be stopped. Review choice of anticoagulant.
Skin reactions	Pruritis can occur with or without rash and usually requires a review of treatment. Minor rashes do not warrant treatment discontinuation, but more severe reactions do. An alternative treatment may be required.
Pain in extremities	May be a sign of haemorrhage or may be idiopathic.
Fever	It is not known if these symptoms are caused by the drug or not, but they have been described in association with rivaroxaban.
Malaise, somnolence, decreased energy/ strength	Review if timeline suggests it may be due to rivaroxaban as likely to negatively impact on compliance.
Epistaxis	These are twice as common with rivaroxaban as with warfarin. Exclude raised BP as contributory factor Review depending on severity. Seek specialist advice if necessary.

9.2.6 Rivaroxaban drug interactions (refer to BNF and SPC)

Rivaroxaban is metabolised by cytochrome P450 and is also a substrate for P-glycoprotein.

Summary of Drug Interactions for Rivaroxaban

Class	Drugs	Effect	Action
Strong P-gp	Dronedarone	Levels of rivaroxaban	Contraindicated

Class	Drugs	Effect	Action
inhibitors and CYP3A4 inhibitors	Ketoconazole Itraconazole Voriconazole Posaconazole HIV protease inhibitors, e.g. Ritonavir	increased by up to 160%	
Moderate CYP3A4 inhibitor	Fluconazole	Levels of rivaroxaban increased by 40%	Not considered clinically significant

Class	Drugs	Effect	Action
Strong CYP3A4 and moderate P-gp inhibitor	Clarithromycin	Levels of rivaroxaban increased by 50%	Not considered clinically significant. No dose reduction required. Monitor closely. Consider use of azithromycin (safer alternative).
Moderate CYP3A4 and P-gp inhibitor	Erythromycin	Levels of erythromycin increased by 30%	Not considered clinically significant. No dose reduction required. Monitor closely. Consider use of azithromycin (safer alternative).
CYP3A4 inducer	Rifampicin Carbamazepine Phenobarbital Phenytoin St John's Wort	Reduces area under curve (AUC) of rivaroxaban by 50% causing a reduced anticoagulation effect	Contraindicated
Others	Aspirin Clopidogrel NSAIDs	Increased risk of bleeding	Combination not recommended. Consider GI protection. Close monitoring for signs of bleeding.
	SSRIs	Increased risk of bleeding	If combination is needed then consider GI protection if not already prescribed.
	Prasugrel Ticagrelor	Increased risk of bleeding	Avoid combination

9.3 Apixaban

2.5 mg and 5 mg tablets are licensed for stroke prevention in non valvular AF.

9.3.1 Dosage

Indication	Dose
Prevention of stroke in patients with non-valvular AF and with a CHA2DS2VASc score of 1 or more for males. **CHA2DS2VASc** of 2 or more for females.	• Apixaban 5 mg twice daily is the usual dose. • All patients with creatinine clearance 15 – 29 ml/min should receive 2.5 mg twice daily of apixaban. In addition, if they meet two of the following criteria they should receive the lower dose: Serum creatinine≥ 133 micromol/L, age ≥80 years or body weight ≤60 kg.

9.3.2 Apixaban missed doses

A forgotten apixaban dose may be taken up to 6 hours after the last scheduled dose. From 6 hours prior to the next scheduled dose onwards, the missed dose should be omitted. No double dose should be taken to make up for missed doses.

9.3.3 Switching from warfarin to apixaban

In patients taking warfarin, stop the warfarin and start apixaban once INR is less than 2.

9.3.4 Switching from apixaban to warfarin

When converting patients from apixaban to warfarin therapy, continue administration of apixaban for at least 2 days after starting warfarin therapy or until INR ≥2. The switching should only be carried out via the anticoagulation clinic.

9.3.5 Apixaban time to response

Apixaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 3 to 4 hours after tablet intake.

9.3.6 Apixaban side effects and actions to be taken (see SPC for full list)

Apixaban is a new drug and is marked ▼ in the BNF which signifies intensive monitoring by the MHRA. Please report all suspected side effects through the yellow card system. There is a lack of long term follow up data available. The following table covers the common side effects listed in the SPC. Other than hypersensitivity reactions and contusions no other adverse reactions are listed in the SPC for apixaban. However experience in real world patients has found similar side effects to rivaroxaban. Please also see adverse reactions listed in the SPC for rivaroxaban to determine if they could be due to the drug and seek advice if severe.

Side Effects	Action
Risk of bleeding	Patients who bleed do not respond to vitamin K and so the majority of the management is supportive care – managed within secondary care. The drug is 25% renally excreted and will accumulate and potentially cause toxicity if prescribed in patients with a severe renal failure. Apixaban is contraindicated if CrCl <15 ml/min - stop the drug and review alternative choices of anticoagulation.
Eye haemorrhage, haematuria, vaginal bleeding, respiratory tract haemorrhage (e.g. alveolar)	Treat symptomatically, seek expert advice if necessary.
Anaemia	If Hb <80 g/L do not start anticoagulation until anaemia has been treated and resolved. If Hb 80 – 100 g/L review the urgency of anticoagulation and seek advice if there is a need to anticoagulate quickly. If Hb 101 g/L or more it is safe to anticoagulate, although treatment of any underlying reasons for anaemia is recommended.
Contusions, dizziness, syncope	Dizziness and syncope are not listed as side effects but these are side effects with rivaroxaban, another anti-Xa inhibitor, and it is possible that blows to the skin as result of these are the cause of the contusions which are a side effect listed in the SPC. Review anticoagulation options. Severe symptoms can result in falls and inability to drive. Even if dizziness and syncope are mild, because they do not improve with time may affect compliance.
Skin reactions	Pruritis can occur with or without rash and usually requires a review of treatment. Minor rashes do not warrant treatment discontinuation, but more severe reactions do. An alternative treatment may be required.
Malaise, somnolence, decreased energy/strength	Review if timeline suggests it may be due to apixaban, as likely to negatively impact on compliance. An alternative anticoagulant may be required.
Epistaxis	More common with apixaban than warfarin. Review depending on severity. Seek specialist advice.

9.3.7 Apixaban drug interactions (refer to BNF and SPC)

Apixaban is metabolised by cytochrome P450 and is also a substrate for P-glycoprotein. In theory, other interactions are possible but many remain unstudied.

Summary of Drug Interactions for Apixaban

Class	Drugs	Effect	Action
Strong CYP3A4 and P-gp inhibitors	Dronedarone Ketoconazole Itraconazole Voriconazole Posaconazole HIV protease inhibitors, e.g. ritonavir	Levels of apixaban increased by 100% for some of these whilst no data is available for others.	Contraindicated
Other moderate or weak inhibitors of CYP3A4, P-gp inhibitors or both	Diltiazem Naproxen Amiodarone Verapamil Quinidine	Levels of apixaban increased but to a lesser extent than with the strong inhibitors.	Monitor for signs of bleeding, no dose adjustment required.
Strong CYP3A4 and P-gp inducers	Rifampicin Phenytoin Carbamazepine Phenobarbital St. John's Wort	Levels of apixaban reduced, 50% reduction with rifampicin.	Combination contraindicated.
Others	Aspirin Clopidogrel NSAIDs	Increased risk of bleeding.	Avoid combination. Consider GI protection. Close monitoring for signs of bleeding.
	SSRIs	Increased risk of bleeding.	If combination needed, consider GI protection if not prescribed.
	Prasugrel Ticagrelor	Increased risk of bleeding.	Avoid combination.

9.4 Edoxaban

9.4.1 Edoxaban is licensed for stroke prevention in non-valvular AF (see SPC for more detailed information)

Indication		Dose
Prevention of stroke in patients with non-valvular AF and with a CHA2DS2VASc of 1 or more for males. **CHA2DS2VASc** of 2 or more for females.		60 mg once daily
Dose recommendation for patients with one or more of the following clinical factors:		
Renal Impairment	Moderate or severe (CrCL 15 – 50 mL/min)	30 mg once daily
Low Body Weight	≤ 60 kg	
P-gp Inhibitors	Ciclosporin, dronedarone, erythromycin, ketoconazole	

NOTE: A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin therefore, edoxaban should only be used in patients

with NVAF and creatinine clearance above 100mL/min after a careful evaluation of the individual thromboembolic and bleeding risk.

9.4.2 Edoxaban missed doses

A forgotten edoxaban dose may be taken as soon as the patient remembers, on the same day. No double dose should be taken to make up for missed doses.

9.4.3 Switching from warfarin to edoxaban

This should be undertaken under secondary care advice.
In patients taking warfarin, stop the warfarin and start edoxaban once INR is ≤ 2.5.

9.4.4 Switching from edoxaban to warfarin

When converting patients from edoxaban to warfarin therapy, continue administration of edoxaban at 50% of previous dose until INR ≥2, (i.e. from 60mg daily to 30mg daily OR 30mg daily to 15mg daily)..

Loading doses of warfarin loading should NOT be administered when switching from edoxaban to warfarin. The switch should only be carried out by the anticoagulation clinic.

9.4.5 Time to response with edoxaban

Full anticoagulation is expected within 1 - 2 hours of initiation.
The half-life is 10 -14 hours and so its effects will completely wear off in 3 days.

9.4.6 Edoxaban side effects and actions to be taken (see SPC for full list)

Edoxaban is a new drug and is marked ▼ in the BNF which signifies intensive monitoring by the MHRA. Please report all suspected side effects through the yellow card system. There is a lack of long term follow up data available. The following table covers the common side effects listed in the SPC.

Side Effects	Action
Risk of bleeding	Patients who bleed do not respond to vitamin K and so the majority of the management is supportive care - seek Haematology advice.. The drug is 50% renally excreted and will accumulate and potentially cause toxicity if prescribed in patients with a severe renal failure. Edoxaban is contraindicated if CrCl <15 ml/min - stop the drug and review alternative choices of anticoagulation.
Mucosal bleeding (e.g. epistaxis, gastrointestinal, genitourinary)	Mucosal bleedings are seen more frequently during long term edoxaban treatment compared with VKA treatment. Treat symptomatically, seek expert advice if necessary.
Anaemia	If Hb <80 g/L do not start anticoagulation until anaemia has been treated and resolved. If Hb 80 – 100 g/L review the urgency of anticoagulation and seek advice if there is a need to anticoagulate quickly. If Hb 101 g/L or more it is safe to anticoagulate, although treatment of any underlying reasons for anaemia is recommended.
Dizziness	Dizziness is not listed as side effects but these are side effects with other anti-Xa inhibitor. Monitor for this side effect. Severe symptoms can result in falls and inability to drive. Even if dizziness and syncope are mild, because they do not improve with time may affect compliance.
Skin reactions	Pruritis can occur with or without rash and usually requires a review of treatment. Minor rashes do not warrant treatment discontinuation, but more severe reactions do. An alternative treatment may be required.
Malaise, somnolence, decreased energy/strength	Review if timeline suggests it may be due to edoxaban, as likely to negatively impact on compliance. An alternative anticoagulant may be required.

Epistaxis	More common with edoxaban than warfarin. Check BP to exclude as contributory cause Review depending on severity. Seek specialist advice if necessary.

9.4.7 Edoxaban notable drug interactions (refer to BNF and SPC)

Edoxaban is metabolised by hydrolysis and cytochrome P450 and is also a substrate for P-glycoprotein. In theory, other interactions are possible but many remain unstudied.

Class	Drugs	Effect	Action
Strong CYP3A4 and P-gp inhibitors	Ciclosporin, dronedarone, erythromycin, or ketoconazole	Levels of edoxaban increased	Requires dose reduction to 30 mg once daily
Strong CYP3A4 and P-gp inhibitors BUT no clinical data	Itraconazole Voriconazole Posaconazole HIV protease inhibitors, e.g. ritonavir	Likely increased levels	contraindicated
Class	**Drugs**	**Effect**	**Action**
Other moderate or weak inhibitors of CYP3A4, P-gp inhibitors or both	quinidine, verapamil, or amiodarone	Increased levels of edoxaban	Does not require dose reduction based on clinical data
Strong CYP3A4 and P-gp inducers	Rifampicin Carbamazepine Phenobarbital Phenytoin St John's Wort	Levels of edoxaban reduced, 35%.	Use with caution
Others	Aspirin Clopidogrel NSAIDs	Increased risk of bleeding	Combination not recommended. Consider GI protection. Close monitoring for signs of bleeding.
	SSRIs	Increased risk of bleeding	If combination is needed then consider GI protection if not already prescribed.
	Prasugrel, ticagrelor	Increased risk of bleeding	Avoid combination

10. MANAGEMENT OF OVERDOSE AND BLEEDING

This will occur within secondary care.

11. BACK-UP INFORMATION/ADVICE

Anticoagulation	Contact Details

clinic	**Nurses**	**01183227450 (anticoag. sister) 01183228237 or 01183227366**

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13. Appendices

Appendix A: Creatinine Clearance (ml/min) using Cockcroft & Gault Equation

Female ≥60 kg* creatinine clearance ml/min

age / serum creatinine	40	45	50	55	60	65	70	75	80	85	90	95	100
50	120	114	108	102	96	90	84	78	72	66	60	54	48
60	100	95	90	85	80	75	70	65	60	55	50	45	40
70	86	81	77	73	69	64	60	56	51	47	43	39	34
80	75	71	68	64	60	56	53	49	45	41	38	34	30
90	67	63	60	57	53	50	47	43	40	37	33	30	27
100	60	57	54	51	48	45	42	39	36	33	30	27	24
110	55	52	49	46	44	41	38	35	33	30	27	25	22
120	50	48	45	43	40	38	35	33	30	28	25	23	20
130	46	44	42	39	37	35	32	30	28	25	23	21	18
140	43	41	39	36	34	32	30	28	26	24	21	19	17
150	40	38	36	34	32	30	28	26	24	22	20	18	16
160	38	36	34	32	30	28	26	24	23	21	19	17	15
170	35	34	32	30	28	26	25	23	21	19	18	16	14
180	33	32	30	28	27	25	23	22	20	18	17	15	13
190	32	30	28	27	25	24	22	21	19	17	16	14	13
200	30	29	27	26	24	23	21	20	18	17	15	14	12

Male ≥70 kg* creatinine clearance ml/min

age / serum creatinine	40	45	50	55	60	65	70	75	80	85	90	95	100
50	168	160	151	143	134	126	118	109	101	92	84	76	67
60	140	133	126	119	112	105	98	91	84	77	70	63	56
70	120	114	108	102	96	90	84	78	72	66	60	54	48
80	105	100	95	89	84	79	74	68	63	58	53	47	42
90	93	89	84	79	75	70	65	61	56	51	47	42	37
100	84	80	76	71	67	63	59	55	50	46	42	38	34
110	76	73	69	65	61	57	53	50	46	42	38	34	31
120	70	67	63	60	56	53	49	46	42	39	35	32	28
130	65	61	58	55	52	48	45	42	39	36	32	29	26
140	60	57	54	51	48	45	42	39	36	33	30	27	24
150	56	53	50	48	45	42	39	36	34	31	28	25	22
160	53	50	47	45	42	39	37	34	32	29	26	24	21
170	49	47	44	42	40	37	35	32	30	27	25	22	20
180	47	44	42	40	37	35	33	30	28	26	23	21	19
190	44	42	40	38	35	33	31	29	27	24	22	20	18
200	42	40	38	36	34	32	29	27	25	23	21	19	17

The SPCs for all NOACs specify that creatinine clearance CrCl (Cockroft & Gault) should be used for dosing decisions, not eGFR. **These tables should not be used for patients in acute renal impairment, who are dehydrated or if under the stated weights. In these instances CrCl should be calculated individually (manually or on, e.g. SystmOne>clinical tools>renal calculations, available in the CCG).**

$$\text{CrCl} = \frac{[140 - \text{age(yrs)}] \times \text{ideal body weight or actual if less (kg)}}{\text{Serum creatinine (micromol/L)}} \times 1.2 \text{ for males}$$

*average ideal body weight