313FM.6 APIXABAN DABIGATRAN, EDOXABAN AND RIVAROXABAN FOR NON VALVULAR ATRIAL FIBRILLATION (AF)

Prescribing guidelines - Formulary Traffic Light Status- GREEN

1. SUMMARY

This guideline provides prescribing and monitoring guidance for anticoagulation with direct oral anticoagulants (DOACs) formerly new oral anticoagulants (NOACs) for stroke prevention in adults with atrial fibrillation (AF).

Before prescribing a DOAC to a patient with AF it needs to be confirmed that anticoagulation is indicated based on an individual benefit/risk analysis. The decision about whether to initiate treatment with a DOAC or warfarin should be made after an informed discussion between the prescriber and the patient about the relative risks and benefits of DOACs and warfarin. The individual's absolute benefit of treatment in terms of stroke risk reduction and bleeding risk with any oral anticoagulant drug (OAC) can be assessed using the CHA_2DS_2VASc and HAS-BLED tool respectively.

For patients who are taking warfarin for AF, the potential risks and benefits of switching to a DOAC should be considered in light of factors such as their level of International Normalised Ratio (INR) control, frequency of INR monitoring, adherence to treatment and ability to attend for INR follow up appointments.

2. BACKGROUND FOR USE

Historically warfarin was the oral anticoagulant of choice. However based on large randomised, controlled trials comparing each of the DOACs with warfarin and greater experience in use, DOACs are now considered the preferred first line option for the management of AF especially in older patients in the absence of any contraindications.

Compared with warfarin, all four DOACS have shown consistent efficacy and safety in terms of stroke reduction in patients with AF. Advantages of DOACs include lack of need for INR monitoring a faster onset of action, shorter half-life and simpler dosing. All anticoagulants increase the risk of significant bleeding however, this is comparatively less with DOACs. Before starting any anticoagulant careful consideration of bleeding risk should be undertaken. Tools such as the HAS-BLED score should be used to help quantify the bleeding risk.

The CHA_2DS_2-VASc and HAS-BLED scores share risk factors and, as a result, patients at high risk of stroke (high CHA_2DS_2-VASc score) often also have a high bleeding risk (HAS-BLED score). Steps should be taken to reduce the bleeding risk through a reduction in modifiable risk factors for bleeding such as uncontrolled blood pressure (BP).

3. CRITERIA FOR USE

In line with NICE Guidelines DOACs may be considered as alternatives to warfarin in patients with non-valvular (NV) AF, in whom oral anticoagulation is recommended (i.e. with CHA_2DS_2-VASc ≥1 for men or ≥2 for women). The term 'non valvular AF' refers to AF in the absence of a mechanical prosthetic heart valve or severe mitral stenosis.

All patients with a diagnosis of AF and a CHA_2DS_2-VASc ≥1 for men or ≥2 for women should have an informed discussion about their individual absolute risk for stroke and be given a choice of oral anticoagulant therapy. Patients will usually be offered a choice between warfarin and a DOAC unless there is a contraindication for use of one over the other. **Regular review is essential to support long term adherence to treatment.** Factors affecting patients' decisions and adherence to taking OACs include:

- An understanding of the condition.
- Need for treatment.
- Concerns about the medicine.
- Awareness of the possible consequences of non-adherence.

A counselling checklist is given in Appendix 1.

When all considerations are equal, the most cost effective DOAC should be the first choice. A summary of DOAC prescribing considerations is given in Table 1. See also Decision Making Algorithm: Oral Anticoagulant Choices for Stroke Prevention in AF.

Key Points for DOACs

- No requirement for INR monitoring.
- Compared with warfarin all have a reduced risk of intracranial haemorrhage.
- DOACs have short half-life and so missed doses will have greater loss of anticoagulation than warfarin.
- Idarucizumab is licensed and NICE-approved for dabigatran reversal in adult patients when rapid reversal of its anticoagulant effects is required. Andexanet alfa is a licensed antidote in the reversal of anticoagulant effect of rivaroxaban and apixaban, however this is not NICE approved. There is currently no licensed antidote for the reversal of anticoagulant effect of edoxaban (although products are available to help counteract the anticoagulant effect, such as tranexamic acid and prothrombin complex concentrate).
- Immediate anticoagulant effect (time to peak effect ranges from 1 - 4 hours).
- DOACs currently have no known food interactions and DOAC blood levels not affected by alcohol and significantly less drug-drug interactions (see Table 5 Notable Drug Interactions).
- Useful for patients who have difficulty getting INR measured. Minimum blood tests required for DOACs are urea and electrolytes (U&E) (3 monthly to annually), full blood count (FBC) and liver function tests (LFT) (alanine transaminase (ALT)) annually. Renal function should be assessed and monitored using Cockcroft-Gault formula – creatinine clearance (CrCl).
- Useful for patients with erratic INR not due to non-compliance.
- Apixaban, edoxaban and rivaroxaban are stable in a dosette box and so useful for patients who need external support to take medicines.
- Easier to manage around surgical and other elective procedures.

Key points for warfarin

- Good safety record associated with long term use - been prescribed for more than 50 years.
- Warfarin activity/effect can be measured by an INR and may help give an indication of compliance.
- Easily reversible with vitamin K and effective antidote (prothrombin complex concentrate).
- Warfarin – steady state can take at least a week, but patients are often not therapeutic until 2 - 3 weeks into therapy if loaded slowly.
- Warfarin has many drug-drug and certain food interactions which may require additional INR monitoring.
- Patients may have difficulty around INR monitoring. Correct INR can be difficult to manage despite good compliance in some patients.

- Patient needs regular follow up and blood sampling.
- Cannot be put in a dosette box unless risk assessment has been done and a management plan is in place to manage dose adjustment.
- Warfarin and coagulation factors have long half-lives and therefore missed doses result in less loss of anticoagulation compared to DOACs.
- For patients with ischaemic heart disease (IHD), acute coronary syndrome (ACS) or stents follow Cardiology advice regarding use of antiplatelets.

Patient groups considered to benefit from a DOAC include:

- Patients stating preference for DOAC following an informed discussion with a healthcare professional on individual benefits and risks, taking into account their personal circumstances and social needs.
- Polypharmacy patients or patients taking interacting medications.
- Elderly frail and/or housebound patients.
- Patients requiring medication in monitored dosage systems (MDS) - exception to this is dabigatran as this is not suitable for dispensing into a MDS due to drug instability.
- Co-morbidities which are likely to make INR control challenging (clinically unstable or medically complex), e.g. unstable severe chronic obstructive pulmonary disease (COPD), uncontrolled left ventricular failure (LVF), recurrent cellulitis.
- Adherence to variable dosage regimens is likely to be poor, e.g. learning disabilities.
- Those with poor INR control on warfarin despite good compliance.

Patient groups considered suitable for warfarin include:

- Patients taking warfarin for indications other than for anticoagulation in non-valvular AF, unless licensed in these groups.
- Patients with co-existing severe mitral valve disease/stenosis or mechanical heart valve replacements (unlicensed in this group even if the patient has co-existing AF).
- Patients with weight >120 kg (Body Mass Index (BMI) >40 kg/m^2) or <45 kg (BMI <20 kg/m^2).
- Patient with co-existing antiphospholipid antibody syndrome.
- Contraindication to a DOAC.
- Severe or intolerable side effects on DOAC.
- Elevated liver enzymes e.g. ALT >2 - 3 x upper limit of normal (ULN).
- CrCl <15 mL/min as per Cockcroft-Gault equation.
- Patients well controlled on warfarin and stating a preference to remain on warfarin following an informed discussion on their risks and benefits and individual circumstances and needs.
- Patients with a history of poor compliance with medication and would benefit from being able to monitor adherence by regular INR monitoring.

4. TABLE 1: CONSIDERATIONS WHEN DECIDING WHICH OAC FOR AF (see also Decision Making Algorithm: Oral Anticoagulant Choices for Stroke Prevention in AF)

Patient Characteristics	Recommended OAC	Rationale
Mechanical valve or AF with severe mitral stenosis	Warfarin	NOACs are contraindicated for any patient with a mechanical valve.
High risk of bleeding or patient's concern about bleeding	Apixaban Dabigatran 110 mg Edoxaban Rivaroxaban	Reduced risk of bleeding compared to warfarin with apixaban, dabigatran 110 mg dose, edoxaban and rivaroxaban.
History of gastrointestinal (GI) bleed	Apixaban Dabigatran 110 mg Warfarin	Higher rates of GI bleeding with dabigatran 150 mg, rivaroxaban and edoxaban 60 mg compared to warfarin
Dyspepsia	Apixaban Edoxaban Rivaroxaban Warfarin	Dyspepsia reported to occur in 10% of patients on dabigatran – consider cover with proton pump inhibitor (PPI) if using dabigatran
Stroke/transient ischaemic attack (TIA) whilst on warfarin and aged <80 years	Dabigatran	Dabigatran 150 mg BD is the only DOAC shown to be superior to well controlled warfarin in reducing ischaemic stroke. (Dabigatran 110 mg dose non-inferior to warfarin.)
Severe renal impairment (CrCl <30 mL/min)	Apixaban Warfarin	Dabigatran contraindicated. Apixaban, rivaroxaban and edoxaban – lower doses have been approved for patients with CrCl 15 - 30 mL/min. Apixaban is the least renally cleared and recommended by NICE for chronic kidney disease (CKD) patients.
Moderate renal impairment (CrCl 30 - 50 mL/min)	Apixaban Rivaroxaban 15 mg Edoxaban 30 mg	Factor Xa inhibitors less affected by impaired renal function than dabigatran (renal excretion 80% for dabigatran, 50% for edoxaban, 33% for rivaroxaban and 27% for apixaban).
Liver impairment - ALT >x 2 ULN	Warfarin Rivaroxaban (<3 x ULN)	Warfarin is the preferred choice. Patients with elevated liver enzymes (ALT >2 x ULN and 3 x ULN for rivaroxaban) were excluded in DOAC clinical trials.
Mucous membrane bleeding (includes nosebleeds, haematuria, vaginal bleeding)	Dabigatran	Mucous membrane bleeding is more common with factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) compared with warfarin. Mucous membrane bleeding risk is similar with dabigatran and warfarin.
Weight >120 kg or BMI >40 kg/m^2	Warfarin	
Concurrent treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) or prevention of recurrent venous thromboembolism (VTE)	Apixaban Dabigatran Edoxaban Rivaroxaban	Dosing strategy for DOACs is different depending on whether it is for treatment or prevention VTE. Patients with history of VTE and AF should be prescribed the appropriate treatment doses for DOACs. Target INR for warfarin is same for prevention or treatment of VTE as for AF.
Poor compliance with twice daily dosing	Edoxaban Rivaroxaban Warfarin	Only DOACs that are once daily administration.
Patient requiring a monitored dosage system supplied by pharmacy	Apixaban or Edoxaban	Dabigatran not stable in a compliance aid. Rivaroxaban not recommended as first line option unless patient can identify the tablet as needs to be taken with food or a meal.
Patient with coronary artery disease (CAD), history of myocardial infarction (MI) or high risk ACS/MI	Rivaroxaban	Rivaroxaban has been demonstrated to have a positive effect in ACS
Patient with major gastrointestinal resections or bypass	Warfarin	There have been no pharmacokinetic or clinical studies assessing efficacy of DOACs in this cohort.

Patient Characteristics	Recommended OAC	Rationale
Swallowing difficulties or requiring administration via gastric tubes.	Apixaban Edoxaban Rivaroxaban Warfarin	• Dabigatran capsules need to be swallowed whole. Opening the capsules results in a significant increase in bioavailability. • Apixaban tablets may be crushed and suspended in water or apple juice or mixed with apple puree and immediately administered orally. Alternatively, apixaban tablets may be crushed and suspended in 60 mL of water and delivered through a nasogastric tube. • Edoxaban can be crushed and mixed with water or apple puree prior to administration or alternatively crushed and suspended in water and delivered via nasogastric tube. • Rivaroxaban can be crushed and mixed with water or apple puree immediately prior to administration. The dose should immediately be followed by food with some fat content. Rivaroxaban may also be given via gastric tube. • Most brands of warfarin tablets will disperse in water within 5 minutes if shaken and resulting dispersion flushes via fine bore feeding tube without blockage. **In all cases, crushing of tablets and administration via gastric tube is an off label use of all DOACs.**

5. CONTRAINDICATIONS AND PRECAUTIONS

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

Absolute contraindications to warfarin and DOACs:

- Known large oesophageal varices.
- Significant thrombocytopenia (platelet count <50 x 10^9/L) - *refer to haematologist.*
- Within 72 hours of major surgery with risk of severe bleeding - *defer and reassess risk post-operatively.*
- Previously documented hypersensitivity to either the drug or excipients – *consider Cardiology opinion.*
- Acute clinically significant bleed - *defer and once bleeding has stopped reassess stroke versus bleeding risk. Important factors in making this decision will include location of bleed.*
- Decompensated liver disease or deranged baseline clotting screen (INR ≥1.5) – *refer to Gastroenterology/Hepatology. Contraindication applies to oral anticoagulants only.*
- Pregnancy or within 48 hours postpartum - *seek urgent haematological advice. Contraindication applies to oral anticoagulants only.*
- Severe renal impairment. *Contraindication applies to dabigatran with CrCl <30 mL/min and to apixaban, rivaroxaban and edoxaban with CrCl <15 mL/min.*

Relative contraindications to both warfarin and NOACs:

- Previous history intracranial haemorrhage - *some AF patients especially those considered at higher stroke risk (i.e. $CHADS_2$ score ≥3) may benefit from anticoagulation therapy, seek the opinion of a stroke specialist.*
- Recent major extracranial bleed within the last 6 months where the cause has not been identified or treated – *decision for oral anticoagulation therapy should be discussed with specialist*
- Recent documented peptic ulcer (PU) within last 3 months – *decision for oral anticoagulation therapy should be discussed with gastroenterology. In all cases with history of PU, give PPI cover whilst on anticoagulation.*
- 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, glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 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 10^9/L or a thrombocytopenia or anaemia of undiagnosed cause.
- On concomitant drugs associated with an increased bleeding risk, e.g. selective serotonin reuptake inhibitors (SSRIs), oral steroids, non-steroidal anti-inflammatory drugs (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% ($CHADS_2$ score 2 - 3) would need to fall 295 times for fall risk to outweigh stroke reduction benefit of warfarin).

- Dementia or marked cognitive impairment with poor medicines compliance and no access to carer support.
- Chronic alcohol abuse – especially if associated with binge drinking.

Contraindications for DOACs but not for warfarin:

- Patients with co-existing severe mitral valve disease or mechanical heart valve replacements ***(absolute contraindication in this group even if the patient has co-existing AF).***
- Patient with history of antiphospholipid syndrome (relative contraindication) - seek specialist advice.
- Severe renal impairment (CrCl <30 mL/min for dabigatran; CrCl <15 mL/min for edoxaban rivaroxaban or apixaban).
- Patients on concomitant clinically significant interacting drugs – see individual SPC (available on http://www.medicines.org.uk/ ESC Practical Guide on use of non-vitamin K antagonists for further information and advice.
- Not recommended in patients with elevated liver enzymes >2 x ULN – seek specialist advice.
- Patients with a BMI >40 kg/m^2 or weight >120 kg (not recommended).

6. PRE-TREATMENT ASSESSMENT

Baseline weight, U&Es, LFTs (ALT + bilirubin adequate), FBC, BP and pulse check.

U&Es and weight within the last 3 - 6 months are acceptable to calculate CrCl using the Cockcroft-Gault method using actual body weight if the patient's renal function is stable.

FBC within last 6 months may be acceptable but more recent results are required for patients who are frail or at increased bleeding risk e.g. due to concomitant drugs.

It is important to remember the CrCl is only an estimate and should not be considered in isolation. Decisions on dosing should always take into account the renal function trend in conjunction with an estimate of their absolute stroke risk and bleeding risk with anticoagulation.

A suggested counselling checklist is included in Appendix 1.

7. RECOMMENDED ONGOING MONITORING OF ANTICOAGULATION

Monitoring the INR is not required for patients taking DOACs. In line with good anticoagulation practice and national guidance, all patients prescribed a DOAC should be reviewed at least annually to reassess benefits and risks of ongoing therapy.

At each visit:

- Check adherence and patient's understanding on the drug's use and reinforce advice regarding the importance of compliance and what to do in the event of a missed dose.
- Enquire about any adverse effects particularly signs of bleeding.
- Check for any changes in medication including over the counter (OTC) medicines and supplements including oral NSAIDs and aspirin containing products which may have a direct or indirect clinical effect on treatment with DOAC (see ESC Practical guide on use of non-vitamin K antagonists and individual SPC for DOACs for further information).
- Ensure patients taking a DOAC and any carers are clear on the ongoing follow up requirements for their anticoagulation therapy (see Table 2).

Frequency of monitoring renal function in patients prescribed DOACs
The current consensus is that renal function should be assessed at least once a year. The frequency of ongoing monitoring of renal function should be determined by the patient's baseline renal function status and frailty. Any dosage adjustments should be made in line with the individual DOAC licensed recommendations for use.

The European Heart Rhythm Association suggests that if the CrCl is less than 60 mL/minute, the frequency of monitoring (in months) can be guided by the CrCl divided by 10. For example, if the creatinine clearance is 34 mL/minute then the renal function should be monitored every 3 - 4 months.

Currently edoxaban and rivaroxaban are still black triangle status and subject to more intensive monitoring by the MHRA and CHM; all adverse reactions however minor should be reported via the yellow card system. Serious adverse reactions should be reported to the MHRA/CHM for apixaban and dabigatran.

8. TABLE 2: CHECKLIST SUMMARY OF RECOMMENDED FOLLOW UP MONITORING FOR AF PATIENTS ON DOACs

	Interval	Comments
1. Adherence	Each visit and at least annually NICE recommend 3 monthly checks	Assess individual compliance (Rx uptake). Re-educate on importance of strict intake schedule and what to do if dose is missed. Inform and consider adherence aids (drug reminder chart, dosette boxes, smartphone apps). Remind patient to carry OAC alert card at all times.
2. U&Es (creatinine)	According to CrCl but at least annually	More frequently if patient acutely unwell or has evidence of renal impairment or a change in renal function suspected: • CrCl >60 mL/min: Annually. Consider 6 monthly if aged >75 years and frail. • CrCl 30 – 60 mL/min: 6 monthly. • CrCl <30 mL/min: 3 monthly.
3. BP	At least annually	Monitor more frequently if systolic 160 mmHg or above.
4. FBC	At least annually	6 monthly if frail and age >75 years and/or if taking drugs that increase GI bleeding risks or if anaemia is suspected clinically.
5. LFTs as ALT	At least annually	If ALT exceeds 2 x ULN seek further specialist advice.
6. Weight	At least annually	If patient in care home or at extremes of body weight check more frequently.
7. Side effects/ bleeding	Each visit and at least annually	Check within one month of initiation of DOAC and then at least annually. Screen for any unexplained bleeding/bruising which may warrant further follow up.
8. Stroke vs bleeding risk assessment	At least annually	Minimise any modifiable risk factors for bleeding especially uncontrolled hypertension (systolic >160 mmHg), medication or OTC predisposing to bleeding (e.g. reviewing ongoing need for antiplatelets SSRIs excessive alcohol intake). Initiate PPI cover if on dabigatran or rivaroxaban and/or high GI bleeding risk or if previous peptic ulcer.
9. Assess for optimal DOAC and correct dosing	Same monitoring frequency as renal function	Check that the most appropriate DOAC and correct dose has been chosen and there is no change in medical status or concomitant drug therapy warranting a further review. Where patient is borderline for dose a reduction, take into account the individual's current stroke and bleeding risk and renal function trend and whether an alternative DOAC may be more appropriate cover.

9. MISSED DOSES

For DOACs with a twice daily dosing regimen, the forgotten dose can be taken up until 6 hours prior to the next scheduled dose and then continue with twice daily as before. If the next scheduled dose is less than 6 hours, the missed dose should ideally be taken immediately, and a further dose staggered at least 6 hours later.

For DOACs with once daily dosing regimen, the forgotten dose can be taken up to 12 hours prior to the next scheduled dose and/or as soon as the patient remembers and then continued on the following day ensuring at least 12 hours apart between doses. For once a day dosing regimens, the dose should **not** be doubled within the same day to make up for a missed dose.

10. OVERDOSE

Depending on the amount of suspected overdose, hospitalisation for monitoring may be required.

In an emergency situation the action of dabigatran can be reversed by use of idarucizumab (Praxbind®) injection or infusion which is licenced for use in the UK. This agent potently and specifically binds to dabigatran and its metabolites and neutralises their anticoagulant effect. Where indicated, dabigatran treatment can be re-initiated 24 hours after administration of idarucizumab if the patient is clinically stable and adequate haemostasis has been achieved. Idarucizumab does not reverse the effects of any other anticoagulant.

Andexanet alfa, a novel modified recombinant human factor Xa (FXa), rapidly reverses the anticoagulation effects of the factor Xa inhibitors apixaban and rivaroxaban (not licensed for edoxaban) but is not currently on the Buckinghamshire formulary.

11. SWITCHING BETWEEN ORAL ANTICOAGULANTS

- When switching between different anticoagulant regimens, it is important to ensure the continuation of anticoagulant therapy while minimising the risk of bleeding.
- When switching from one DOAC to another DOAC, the alternative DOAC can be initiated when the next dose is due. Patients must not be on more than one drug at once.
- When switching between a parental anticoagulant and a DOAC, start the new OAC when dose of previous drug would have been due.
- For switching from warfarin to DOAC and vice versa, see further supporting information below under relevant DOAC.

12. MANAGEMENT OF DOACs FOR PATIENTS UNDERGOING PLANNED ELECTIVE PROCEDURES OR SURGERY

It is the responsibility of the surgical or medical team performing the elective procedure or surgery to assess the need to interrupt anticoagulant therapy based on the bleeding risk associated with the operation or procedure.

Refer to:
Guideline 34FM Dabigatran: Guidance for Management of Overdose, Bleeding and Emergency/Elective Surgery

Guideline 240FM Rivaroxaban and Apixaban: Guidance for Management of Overdose, Bleeding and Emergency/Elective Surgery

For edoxaban follow the guidance as per rivaroxaban.

Perioperative bridging with low molecular weight heparin is generally not recommended in DOAC treated patients.

13. SUPPORTING INFORMATION FOR INDIVIDUAL DOACs

	Rivaroxaban	**Edoxaban**	**Apixaban**	**Dabigatran**
	Direct factor Xa Inhibitors			Direct thrombin inhibitor
Baseline checks	Renal function using Cockroft-Gault (CrCl) - serum creatinine (Cr) and bodyweight, FBC to include platelets and haemoglobin (Hb), LFTs at least ALT, preferably with bilirubin. Ideally all bloods should be within last 3 - 6 months.			
Prevention of stroke in patients with non-valvular AF and with a CHA_2DS_2VASc of 1 or more for males. CHA_2DS_2VASc of 2 or more for females	**20 mg once daily** Take with or after food to increase bioavailability, consider ability to comply with routine meals.	**60 mg once daily**	**5 mg twice daily**	**150 mg twice daily** Preferably with or after food to minimise gastrointestinal side effects.
Dose adjustments	**15 mg once daily** • CrCl 15 – 49 mL/minute	**30 mg once daily** • CrCl 15 – 49 mL/minute • Low body weight ≤60 kg • P-gp inhibitors (ciclosporin, dronedarone, erythromycin ketoconazole)	**2.5 mg twice daily** • Creatinine clearance 15 – 29 mL/min **OR** • **<u>Two</u>** of the following criteria: – Serum creatinine ≥133 micromol/L – Age ≥80 years **OR** – Body weight ≤60 kg.	**110 mg twice daily** • CrCl 30 - 50 mL/minute • Over 80 • Taking verapamil • High risk of bleeds • Over 75 **and** considered a moderate risk of a bleed • Very low body weight • Concurrent antiplatelet agents Clinical discretion and individual patient factors should be taken into account
MDS/dosette systems	Suitable if dose at a meal time	Yes	Yes	No, dabigatran is hygroscopic (absorbs moisture).

	Rivaroxaban	Edoxaban	Apixaban	Dabigatran
Contraindications	• Active clinically significant bleeding or significant risk for major bleed (see SPC). • Pregnancy and breastfeeding • Concern with GI absorption e.g. bariatric surgery/small bowel resection • High BMI >40 kg/m^2 or weight >120 kg. For patients 120 - 150 kg seek specialist advice.			
	• **CrCl <15 mL/min**			• **CrCl <30ml/min**
	• Hepatic disease associated with coagulopathy and bleeding risk/severe hepatic impairment (ALT/AST >3 x ULN or total bilirubin ≥2.5 x ULN) • Weight >150 kg	• Uncontrolled severe hypertension. • CrCl >100 mL/min. 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 100 mL/min on specialist advice	• Hepatic disease associated with coagulopathy and bleeding risk/severe hepatic impairment (ALT/AST >3 x ULN or total bilirubin ≥2.5 x ULN)	• Hepatic disease associated with coagulopathy and bleeding risk/severe hepatic impairment (ALT/AST >2 x ULN or total bilirubin ≥2.5 x ULN)
Cautions	• CrCl <30 ml/min. • Weight >120 kg, may require peak and trough rivaroxaban levels to evaluate whether therapeutic levels being achieved – seek specialist advice.	• Patients with elevated liver enzymes ALT/AST >2 x ULN or total bilirubin ≥1.5 x ULN were excluded in clinical trials. Use with caution in this population.		
Side effects	See Table 4 Check BNF: https://bnf.nice.org.uk/; For individual SPCs see: www.medicines.org.uk			
Drug interactions	See Table 5 Check BNF: https://bnf.nice.org.uk/; For individual SPCs see: www.medicines.org.uk			
Switching from warfarin	Stop warfarin. Start DOAC when INR ≤3	Stop warfarin. Start DOAC when INR ≤2.5	Stop warfarin. Start DOAC when INR ≤2.5	Stop warfarin • If INR <2 start dabigatran the same day • If INR 2 – 3 start dabigatran the next day • If INR >3 ensure INR is <3 before starting dabigatran as above

	Rivaroxaban	Edoxaban	Apixaban	Dabigatran
Switching to warfarin	Warfarin should only be started by a clinician with expertise in anticoagulation management. The effect of warfarin is only seen after at least a few days and steady state can take at least 7 - 10 days. Unless immediate cessation is necessary the schedules below should be followed. Loading doses are not routinely used when switching from a DOAC to warfarin.			
	Day 1 Warfarin + Rivaroxaban Day 2 Warfarin + Rivaroxaban Day 3 Check INR immediately before next dose rivaroxaban is due. Continue concomitant treatment until INR ≥2 with daily INR checks prior to administration of rivaroxaban. Once INR is in range stop rivaroxaban.	Day 1 Warfarin + Edoxaban at 50% of previous dose until INR ≥2 (i.e. from 60 mg daily to 30 mg daily OR 30 mg daily to 15 mg daily). Check INR a minimum of 3 times and immediately prior to dose of edoxaban. INR ≥2 Continue warfarin only. Stop edoxaban. 2 - 3 days after stopping combined therapy check INR. (To confirm INR is within therapeutic range. Concomitant edoxaban and warfarin can increase the INR post edoxaban dose by up to 46%). Edoxaban prolongs clotting time in tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) at therapeutic doses.	Day 1 Warfarin + Apixaban Day 2 Warfarin + Apixaban Day 3 onwards Warfarin +Apixaban until INR ≥2 (preferred) OR Warfarin only. Stop apixaban.	<u>CrCl ≥50 mL/min</u> Days 1 - 3 Warfarin + Dabigatran Day 4 onwards Warfarin only Stop dabigatran Day 6 onwards Check INR <u>CrCl 30 - 50 mL/min</u>, start Days 1+2 Warfarin + Dabigatran Day 3 onwards Warfarin only Stop dabigatran Day 5 onwards Check INR Dabigatran can contribute to an elevated INR. INR testing should **not** be performed until dabigatran has been stopped for at least 2 days.
Missed doses	If a dose is missed, patient should take it immediately. However, if it is less than 12 hours until the next dose, skip the dose missed and take the next scheduled dose as normal.		If a dose is missed, the patient should take it immediately and then continue with twice daily intake as before. If it is less than 6 hours until the next dose, skip the dose missed and take the next scheduled dose as normal.	
Time to response	Full anticoagulation is expected within 2 - 4 hours of initiation.	Full anticoagulation is expected within 1 - 2 hours of initiation.	Full anticoagulation is expected within 3 to 4 hours after tablet intake.	Full anticoagulation is expected within 1 - 3 hours of initiation.

	Rivaroxaban	Edoxaban	Apixaban	Dabigatran
Half-life	11 - 13 hours in the elderly. 5 - 9 hours in the young.	10 - 14 hours (effects will completely wear off in 3 days)	12 hours	14 - 17 hours
Bioavailability	Almost 100% with food. 66% without food.	62%	Approx 50%	6%
Swallowing difficulties or requiring administration via gastric tubes	Rivaroxaban can be crushed and mixed with water or apple puree prior to administration. The dose should be given with or after fat containing food. Rivaroxaban may also be suspended in water and given via gastric tube.	Edoxaban can be crushed and mixed with water or apple puree prior to administration or alternatively crushed and suspended in water and delivered via a nasogastric tube.	Apixaban tablets may be crushed and suspended in water or apple juice or mixed with apple puree and administered orally. Alternatively, tablets can be crushed and suspended in water and delivered via a nasogastric tube.	Dabigatran capsules need to be swallowed whole. Opening the capsules results in a significant increase in bioavailability.
Hepatic impairment	Contraindicated in severe hepatic impairment. Not recommended if ALT >3 x ULN. (Patients with elevated liver enzymes ALT/AST >3 x ULN were excluded in ROCKET AF trial).	Contraindicated in severe hepatic impairment. Not recommended if ALT >2 x ULN. (Patients with elevated liver enzymes ALT/AST >2 x ULN were excluded in ENGAGE AF trial).	Contraindicated in severe hepatic impairment. Not recommended if ALT >2 x ULN. (Patients with elevated liver enzymes ALT/AST >2 x ULN were excluded in ARISTOTLE AF trial.)	Contraindicated in severe hepatic impairment. Not recommended if ALT >2 x ULN. (Patients with elevated liver enzymes ALT/AST >2 x ULN were excluded in RE-LY AF trial.)
Renal information	The drug is 33% renally excreted.	The drug is 50% renally excreted.	The drug is 25% renally excreted.	The drug is 80% renally excreted.
	Accumulation will occur and potentially cause toxicity if prescribed in patients with a severe renal failure. Anti Xa DOACs are contraindicated if CrCl <15 mL/min - stop the drug and review alternative choices of anticoagulation.			Accumulation will occur 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.

14. COMMON SIDE EFFECTS

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. Rivaroxaban is marked ▼ in the BNF which signifies requiring more intensive monitoring by the MHRA.

Table 4: Management of Common Side Effects (For full list also see BNF: https://bnf.nice.org.uk/ and SPC: www.medicines.org.uk)

Side Effect	Rivaroxaban	Edoxaban	Apixaban	Dabigatran
Dyspepsia, abdominal pain, nausea and diarrhoea				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 H2 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. Its effect wears off over 1 - 2 days. For full management see Trust Guideline 34FM Dabigatran: Guidance for Management of Overdose and Bleeding.
Risk of bleeding	See Trust Guideline 240FM Rivaroxaban and Apixaban: Guidance for Management of Overdose and Bleeding See Trust Guideline 34FM Dabigatran: Guidance for Management of Overdose and Bleeding For Edoxaban follow guidance for rivaroxaban. Interacting drugs may also increase DOAC levels and therefore risk of bleeding.			Patients who bleed maybe treated with idarucizumab (Praxbind)
Anaemia	If Hb <80 g/L cause of anaemia should be investigated. Active bleeding is a contraindication to anticoagulation however, anaemia itself does not preclude the use of anticoagulants and depends on the cause - seek specialist input if required. Urgency of anticoagulation is a key factor. If Hb 80 – 100 g/L review the urgency of anticoagulation and seek advice if there is a need to anticoagulate quickly. If Hb >100 g/L or 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 consider stopping dabigatran and/or seek further specialist advice.

Side Effect	Rivaroxaban	Edoxaban	Apixaban	Dabigatran
Myocardial infarction (MI) or ischaemic heart disease (IHD)				There was a statistically insignificant increased number of MIs in the dabigatran arm of RE-LY. Ideally choose alternative DOAC in patients with a past history of IHD; review benefits versus risks if there is a compelling need to treat.
Dizziness, headache, syncope	Dizziness and syncope are not listed as side effects of edoxaban and apixaban but they are side effects with rivaroxaban, it is possible that blows to the skin as a result of these are the cause of the contusions which are a side effect listed in the SPC. 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. Review anticoagulation options.			
Eye haemorrhage, haematuria, vaginal bleeding	Mucosal bleedings are seen more frequently during long term anti Xa treatment compared with vitamin K antagonist treatment. Treat symptomatically, seek expert advice if necessary.			
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 DOAC. If patient was asymptomatic with AF more likely to be drug related. An alternative DOAC is worth considering as likely to negatively impact on compliance.			
Epistaxis	These are more common with edoxaban and apixaban than with warfarin and twice as common with rivaroxaban as with warfarin. They are less common with dabigatran than anti Xa DOACs. Exclude raised BP as contributory factor. In most patients it is safe to continue treatment. Review depending on severity. If clinically concerned about acute or recurrent epistaxis seek specialist advice.			
Oedema	Review, especially if increasing shortness of breath or oedema.			
Tachycardia	Unless clinically worrying does not require action.			
Pain in extremities	May be a sign of haemorrhage or may be idiopathic.			
Fever	Unknown if these symptoms are caused by the drug but they have been described in association with rivaroxaban.			

15. NOTABLE DRUG INTERACTIONS

Although DOACs have fewer drug interactions than warfarin drug interactions with the P-glycoprotein (P-gp) and CYP450 3A4 enzymes become important considerations with these drugs.

The European Society of Cardiology has produced a useful practical guide on prescribing DOACs which gives information on the effect of drug to drug interactions and clinical factors on DOAC drug levels – see https://academic.oup.com/eurheartj/article/39/16/1330/4942493 and **individual DOAC summary product characteristics on emc medicines website.**

All DOAC metabolism is affected by P-gp such to the extent that they are not recommended to be given with P-gp inducers, rifampicin being the most potent interaction cited due to its ability to decrease anticoagulant efficacy. However, inhibitors of P-gp can increase systemic exposure from DOACs and thereby increase bleeding risk. Dabigatran and edoxaban are mainly metabolised by P-gp, and dose reductions are recommended based on indication (NVAF or VTE) when renal function is impaired (an additional risk for bleeding). Rivaroxaban and apixaban are also metabolised through the liver and require dose adjustment to avoid bleeding risk when combined with strong CYP450 3A4 and P-gp inhibitors.

Table 5: DOAC Notable Drug Interactions (Please also see BNF: https://bnf.nice.org.uk/; SPC: www.medicines.org.uk)

Class	Drugs	Rivaroxaban	Edoxaban	Apixaban	Dabigatran
		Rivaroxaban is metabolised by cytochrome P450 and is also a substrate for P-glycoprotein. Interactions can occur with inhibitors or inducers of both P-gp and CYP3A4.	Edoxaban is metabolised by hydrolysis and cytochrome P450 and is also a substrate for P-glycoprotein. Interactions can occur with inhibitors or inducers of both P-gp and CYP3A4.	Apixaban is metabolised by cytochrome P450 and is also a substrate for P-glycoprotein. Interactions can occur with inhibitors or inducers of both P-gp and CYP3A4.	Dabigatran is a pro-drug not metabolised by the cytochrome P450 system and has no *in vitro* effects on human cytochrome P450 enzymes. Dabigatran is however a substrate at P-glycoprotein receptors (P-gp). Interaction can occur with P-gp inhibitors or inducers.
Strong inhibitors of P-gp and CYP3A4	Ketoconazole Itraconazole Posaconazole Voriconazole (see below for fluconazole)	Levels of rivaroxaban increased by up to 160%. Contraindicated	Levels of edoxaban likely to increase. Ketoconazole requires dose reduction to 30 mg once daily.	Levels of apixaban increased by 100% for some, no data available for others. Contraindicated.	Levels of dabigatran increased. Levels of dabigatran increased by ~150% for ketoconazole. Contraindicated.
Strong P-gp inhibitor and moderate CYP3A4 inhibitor	Dronedarone	Levels of rivaroxaban increased by up to 160%. Contraindicated.	Levels of edoxaban likely to increase. Requires dose reduction to 30 mg once daily.	Levels of apixaban increased by 100% for some, no data available for others. Contraindicated.	Levels of dabigatran increased by ~100% for dronedarone. Contraindicated.
Strong P-gp inhibitor/inducer and strong inhibitor of CYP3A40	HIV protease inhibitors	Levels of rivaroxaban increased by up to 160%. Contraindicated.	Levels of edoxaban likely to increase. Contraindicated.	Levels of apixaban increased by 100% for some, no data available for others. Contraindicated.	May increase or decrease risk of bleeding. Avoid combination.

Class	Drugs	Rivaroxaban	Edoxaban	Apixaban	Dabigatran
Strong P-gp inhibitors and moderate CYP3A4 inhibitors	Ciclosporin	Predicted to increase exposure, increasing rivaroxaban effect.	Levels of edoxaban increased. Requires dose reduction to 30 mg once daily.	Predicted to increase exposure, increasing apixaban effect.	Contraindicated.
	Tacrolimus	Extent of interaction unknown.	Interaction expected. Avoid.	Extent of interaction unknown.	Combination contraindicated.
Mild to moderate P-gp inhibitor and moderate CYP3A4 inhibitor	Amiodarone Quinidine Verapamil		Levels of edoxaban increased. Does not require dose reduction based on clinical data.	Levels of apixaban increased but to a lesser extent than with the strong inhibitors. Monitor for signs of bleeding, no dose adjustment required.	Levels of dabigatran increased by ~50 - 60%. Reduce dose to 110 mg twice daily. 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 twice daily, 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.
	Diltiazem			Levels of apixaban increased but to a lesser extent than with the strong inhibitors. Monitor for signs of bleeding, no dose adjustment required.	
Moderate CYP3A4 inhibitor	Fluconazole	Levels of rivaroxaban increased by 40%. Not considered clinically significant.	No data	Not considered clinically significant.	No data

Class	Drugs	Rivaroxaban	Edoxaban	Apixaban	Dabigatran
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).	Predicted to increase exposure to edoxaban. Not considered clinically significant.	Expected increase in levels of apixaban. Not considered clinically significant.	Levels of dabigatran increased by ~20%. No dose reduction required. Monitor closely. Consider use of azithromycin (safer alternative).
Moderate CYP3A4 and moderate 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).	Levels of edoxaban increased. Requires dose reduction to 30 mg once daily.	Might increase in levels of apixaban. Not considered clinically significant.	Levels of dabigatran increased by ~20%. No dose reduction required. Monitor closely. Consider use of azithromycin (safer alternative).
Strong P-gp inducer and strong CYP3A4 inducer	Rifampicin Carbamazepine Phenytoin Phenobarbital St John's Wort	Reduces area under curve (AUC) of rivaroxaban by 50% causing a reduced anticoagulation effect. Contraindicated.	Levels of edoxaban reduced, 35%. Preference to avoid.	Levels of apixaban reduced, 50% reduction with rifampicin. Combination contraindicated.	Levels of dabigatran decreased. Combination contraindicated.
Others	Aspirin Clopidogrel NSAIDs	Increased risk of bleeding. Combination not recommended. Consider GI protection. Close monitoring for signs of bleeding.	Increased risk of bleeding. Combination not recommended. Consider GI protection. Close monitoring for signs of bleeding.	Increased risk of bleeding. Combination not recommended. Consider GI protection. Close monitoring for signs of bleeding.	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.	Increased risk of bleeding. If combination is needed, then consider GI protection if not already prescribed.	Increased risk of bleeding. If combination is needed, then consider GI protection if not already prescribed.	Increased risk of bleeding. If combination is needed, then consider GI protection if not already prescribed.
	Prasugrel Ticagrelor	Increased risk of bleeding Avoid combination	Increased risk of bleeding Avoid combination	Increased risk of bleeding Avoid combination	Increased risk of bleeding Avoid combination.

16. MANAGEMENT OF OVERDOSE AND BLEEDING

For overdose and bleeding, please see the following guidelines:
Guideline 34FM Dabigatran: Guidance for Management of Overdose, Bleeding and Emergency/Elective Surgery.

Guideline 240FM Rivaroxaban and Apixaban: Guidance for Management of Overdose, Bleeding and Emergency/Elective Surgery

17. BACK-UP INFORMATION/ADVICE

	Contact Details	
	Wycombe and Amersham Hospitals	**Stoke Mandeville Hospital**
BHT Anticoagulant Service	Tel: 01494 425590 Email: buc-tr.bucksnoac@nhs.net	
Cardiology	Dr Piers Clifford piers.clifford1@nhs.net Tel: 01494 425004 Dr Soroosh Firoozan s.firoozan@nhs.net Tel: 01494 425004 Dr Rodney De Palma rodney.depalma@nhs.net Dr Ricardo Petraco Ricardo.petraco@nhs.net Dr Norman Qureshi norman.qureshi2@nhs.net	Dr Andrew Money-Kyrle andrew.mkyrle@nhs.net Tel: 01296 315544 Dr Punit Ramrakha p.ramrakha@nhs.net Tel: 01296 315675
Haematology	In an emergency contact Consultant Haematologist on-call on bleep 6708 via switchboard	In an emergency contact Consultant Haematologist on-call bleep 740 via switchboard
Stroke Specialists	Dr Matthew Burn matthewburn@nhs.net Tel: 01494 426252 Dr Amulya Misra amulya.misra@nhs.net Tel: 01494 426252 Dr Simmie Manchanda simmie.manchanda@nhs.net Tel:01484 426252	Dr Chris Durkin chris.durkin@nhs.net Tel: 01296 316539 Dr Dennis Briley dennis.briley@nhs.net Tel: 01296 315689
Medicines Resource Centre	01494 425355 bucks.medicinesresourcecentre@nhs.net	
Switchboard	Amersham: 01494 434411 Wycombe: 01494 526161	01296 315000

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7. SPC for Apixaban 5 mg available at https://www.medicines.org.uk/emc/product/2878/smpc
8. SPC for Apixaban 2.5 mg available at https://www.medicines.org.uk/emc/product/4756/smpc
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See also:

Guideline 34FM Dabigatran: Guidance for Management of Overdose, Bleeding and Emergency/Elective Surgery

Guideline 240FM Rivaroxaban and Apixaban: Guidance for Management of Overdose, Bleeding and Emergency/Elective Surgery

Guideline 775FM Treatment of Atrial Fibrillation

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Updated by	Roshni Kotecha, Medicines Optimisation Pharmacist, Buckinghamshire CCG Kirsty Scott, NOAC Pharmacist BHT Dr Renu Riat, Haematology Consultant BHT Dr Piers Clifford, Cardiology Consultant BHT Jane Butterworth: Associate Director Medicines Optimisation Buckinghamshire CCG Shona Lockie: Clinical Director MMT Buckinghamshire CCG Phil Southworth: Associate Director of Pharmacy BHT
SDU(s)/Department(s) responsible for updating the guideline	Pharmacy (Primary and Secondary Care) Haematology Cardiology
Uploaded to Intranet	29th April 2021
Buckinghamshire Healthcare NHS Trust/Buckinghamshire Clinical Commissioning Group	

Appendix 1: Suggested Counselling Checklist

Hospital Number:
NHS Number:
Patient Name:
Date of Birth:

Counselling Points		Sign
1.	**What is anticoagulation and how does it work**	
2.	**Indication for DOAC – explain AF and discuss individual risk for stroke**	
3.	**Alternative anticoagulation options**	
4.	**Advantages and disadvantages of DOAC compared to warfarin**	
5.	**Expected duration of therapy - usually lifelong –** *if for cardioversion/cardiac ablation cover* **only** *check with referrer if unclear*	
6.	**How to take: including dose, frequency, timing** (aim to take at the same times every day) • Rivaroxaban MUST be taken with food to maximise absorption • Apixaban and edoxaban can be taken with/without food. • Dabigatran: take with food to minimise indigestion; capsules must NOT be opened or chewed and must NOT be removed from original packaging (i.e. do not transfer to dosette)	
7.	**Importance of adherence and persistence with treatment:** • Fairly rapid fall in drug levels (and therefore loss of effectiveness) if poorly compliant • Ways of remembering to take the tablets/capsules e.g. calendar • Important not to stop treatment unless discussed with doctor	
8.	**What to do if a dose is missed -** *If unsure, talk to healthcare provider* • **Once daily** dosing: take within 12 hours of missed dose, if more than 12 hours, omit the dose and then continue at the usual time. • **Twice daily** dosing: take within 6 hours of missed dose, if more than 6 hours, omit the dose and then continue at the usual time.	
9.	**Extra dose taken accidentally?** Contact doctor or healthcare team	
10.	**Possible side effects and what to do if experienced**	
11.	**Monitoring** (e.g. renal function), explain how often and next follow up due *Frequency of monitoring usually depends on the level of renal function (but also other parameters). Also, wt, BP, FBC and LFTs (minimum annually).*	
12.	**Potential for drug interactions**: Avoid over the counter medicines containing aspirin (e.g. flu remedies), NSAIDs (e.g. ibuprofen, naproxen, diclofenac) or herbal/alternative remedies. Paracetamol is the preferred analgesic.	
13.	**Alcohol intake –** recommended limits. *Alcohol not expected to affect DOAC levels per se. Excess alcohol consumption and binge drinking not advised, due to risks of alcohol associated acute injuries (e.g. head injuries) and chronic liver disease (which may affect coagulation). Also at higher risk of GI bleeding.*	
14.	**Importance of reliable contraception in women of childbearing age and need to seek urgent medical advice in case of unexpected pregnancy** (DOACs cross the placenta). **Do not breastfeed.**	
15.	**Procedures** (including day surgery/dental or chiropractic treatments etc.); **hospital admissions** Patient must inform healthcare professional that she/he is taking DOAC. Not necessary to stop DOAC for routine dental procedures.	
16.	**Leisure activities:** Avoid/advise on the risk of contact sports (e.g. football, rugby, boxing) and other higher risk sports (e.g. skiing and horse riding), as increased risk of head injury/falls/bruising/bleeding. Seek urgent medical advice if head injury sustained.	
17.	**Injections** (including immunisation): To inform relevant healthcare provider. Best to have injections/have blood tests ideally before next dose is due as DOAC blood levels lowest.	
18.	**How to obtain further supplies**	
19.	**Who to contact for advice/further information**	
20.	Supply appropriate company DOAC patient information booklet Supply completed OAT or equivalent anticoagulant card – patient to carry at all times	
21.	**Recheck patient's understanding of the above points**	

Appendix 2: Decision Making Algorithm: Oral Anticoagulant Choices for Stroke Prevention in AF

See http://www.bucksformulary.nhs.uk/docs/Guideline_313AFM.pdf