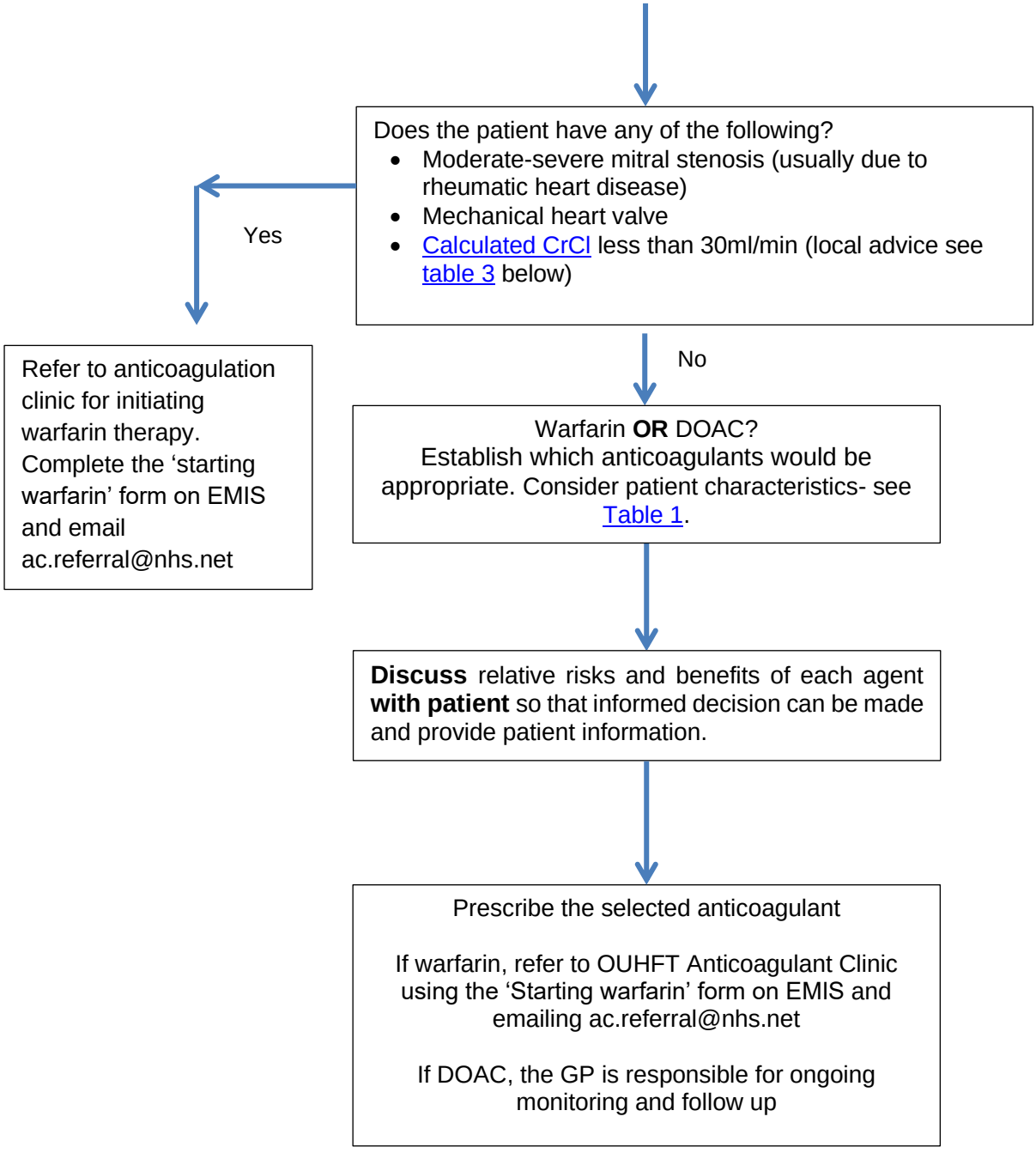
Primary Care Prescriber Decision Support for Direct Oral Anticoagulants 'DOACs' for Stroke Prevention in Atrial Fibrillation

The patient has AF and using the CHA2DS2-VASc and HAS-BLED score the decision has been made to anticoagulate. Anticoagulants continue to be under-prescribed because of a perceived underestimation of the benefits and an over estimation of the risks particularly the risk of bleeding. **Patients on any type of anticoagulant will need education** (http://www.patient.co.uk/health/anticoagulants). This is automatically provided through the Oxfordshire anticoagulation service for patients initiated on warfarin. If the DOACs are initiated in primary care, GPs are responsible for supplying information to patients or they can request this directly with the anticoagulation service **if** discontinuing warfarin. Community pharmacists can provide further education under the New Medicine Service.



Choice of anticoagulant therapy

The decision about whether to start treatment with warfarin or a DOAC should be made after an informed discussion between the prescriber and the patient about the relative risks and benefits of each medicine. DOACs are considered first-line treatment unless contraindications, not tolerated or considered unsuitable.

There are many factors to consider when recommending an anticoagulant. For example, indication, bleeding risk, drug interactions, renal and liver function, lifestyle issues, alcohol consumption, medication adherence and necessity to comply with monitoring arrangements etc.

Key points for warfarin

- Well-established and considerable experience and long-term safety data available.
- Warfarin effect can be measured by an INR and may help give an indication to the level of adherence.
- Effective antidote.
- Steady state can take at least a week, but patients are often not therapeutic until 2-3 weeks into therapy.
- Warfarin has many drug-drug interactions and certain food interactions which may require additional INR monitoring.
- Patients may have difficulty with the practical aspects of INR monitoring. In some patients, therapeutic INR can be difficult to consistently achieve despite good adherence.
- Time in therapeutic range is a measure of warfarin control over the last 6 months.
- Patient needs regular follow up and blood tests.
- Cannot be put in a dosette box unless risk assessment has been done and a management plan is in place to manage dose adjustment.
- Due to the long half-life of warfarin, if a dose is missed, the loss of anticoagulant effect is much slower in comparison to DOACs.
- For patients with IHD, ACS or stents follow Cardiology advice regarding use of antiplatelets.

Key points for DOACs

- No requirement for INR monitoring; useful for patients who have difficulty with INR blood tests e.g. needle phobic, difficult to cannulate etc.
- Over 10 years of experience in clinical practice
- Compared with warfarin all have a reduced risk of intracranial haemorrhage (approximately 50%).
- Idarucizumab is licensed and NICE-approved for dabigatran reversal in adult patients when rapid reversal of its anticoagulant effects is required.
- Andexanet alfa is licensed and NICE approved for reversal of the anticoagulant effect of rivaroxaban and apixaban in life threatening bleeding from the GI tract. Other types of bleeding associated with apixaban or rivaroxaban would be treated with other available products to help counteract the anticoagulant effect e.g. tranexamic acid and prothrombin complex concentrate.
- There is no reversal agent for edoxaban currently available, but other products are accessible to help counteract the anticoagulant effect e.g.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.
- Minimum of U&E and LFT annually. Renal function should be assessed and monitored using Cockcroft and Gault formula – Creatinine Clearance (CrCl), especially in elderly patients (aged 75 years and older) and patients at extremes of muscle mass (BMI less than 18 kg/m^2 or greater than 40 kg/m^2).
- If CrCl is equal to or less than 60 ml/min, recheck patient's renal function at an interval of 'CrCl/10' monthly (e.g. CrCl =44ml/min, 44/10 = monitor every 4 months).
- Useful for patients with erratic INR *not due* to non-adherence
- Apixaban, edoxaban and rivaroxaban are stable in a dosette box and so useful for patients who need support to take medicines.
- DOACs have short half-life and so missed doses will have greater loss of anticoagulation.
- Limited data for using in patients with a body weight of over 120kg or BMI over 40kg/m^2 (see table 1).
- For patients with IHD, ACS or cardiac stents follow Cardiology advice regarding use of antiplatelets.

Patient groups considered to benefit from warfarin include:

- Patients with a weight of more than 120kg or BMI over 40 kg/m^2 (see table below).
- Contraindications to DOACs:
    - Severe renal impairment (dabigatran CrCl less than 30 mL/min, rivaroxaban, apixaban and edoxaban, CrCl less than 15 mL/min, see table 3 for more information).
    - Hepatic impairment (See individual SPCs and table 3 for further advice).
    - Concurrent use of interacting medicines which are potent inducers/inhibitors of CYP3A4 and P-glycoprotein metabolism pathways.
    - Intolerance/allergy to a previous DOAC (depending on the severity of reaction)
- Patients that consider warfarin as their preferred anticoagulant following an informed discussion with a clinician on the risks, benefits, individual circumstances and needs.

Patient groups considered to benefit from a DOAC include:

- Those with poor INR control (TTR less than 65%) on warfarin despite good adherence.
- Significant difficulties with INR monitoring.
- Patients in whom warfarin is unsuitable due to allergy or intolerance e.g. alopecia.
- Those with recurrent changes in medicines which may be influencing INR control.
- Those with monitored dosage systems (MDS) (except dabigatran which is not suitable for use in an MDS).
- Patients that consider a DOAC as their preferred anticoagulant following an informed discussion with a clinician on the risks, benefits, individual circumstances and needs.

Table 1. Considerations when deciding which anticoagulant for which patient

Patient characteristics	Which anticoagulant	Rationale
Mechanical valve or moderate to severe mitral stenosis	Warfarin	DOACs are contraindicated
High risk of bleeding or patients' concern about bleeding	Apixaban Dabigatran 110mg Edoxaban	Reduce risk of bleeding compared to warfarin with apixaban, dabigatran 110mg and edoxaban.
History of GI bleed	Apixaban Dabigatran 110mg Warfarin	Higher rates of GI bleeding with dabigatran 150mg, rivaroxaban and edoxaban 60mg compared to warfarin.
Dyspepsia	Apixaban Rivaroxaban Warfarin Edoxaban	Dyspepsia occurred in 10% of patients on dabigatran
High risk of ischaemic stroke and age < 80 years	Dabigatran 150mg	Dabigatran 150mg bd and apixaban have been shown to be superior to warfarin in reducing ischaemic stroke and systemic embolisation.
Renal impairment – calculated CrCl <30ml/min	Warfarin	DOACs not recommended. Apixaban is the least renally cleared. See table 3 below for more detail.
Liver impairment – AST/ALT more than 2 x ULN	Warfarin	Warfarin is preferred. See table 3 below for more detail.
Once a day formulation preferred	Edoxaban Rivaroxaban Warfarin	Rivaroxaban and edoxaban are both once a day administration (note a missed dose of a once a day preparation extends the time interval between doses more than twice a day regimen)
Requirement for a compliance aid (weekly monitored dosage systems filled by pharmacy, or weekly tablet organiser filled by patient, e.g. Nomad, Dosette, etc.)	Apixaban Edoxaban Rivaroxaban	Dabigatran must be kept in the original packaging with desiccant, therefore is not suitable for use in compliances aids or weekly pill organisers. Warfarin cannot be put in a dosette box unless risk assessment has been done and a management plan is in place to manage dose adjustment.
Swallowing difficulties or requiring administration through gastric tubes	Apixaban Rivaroxaban Warfarin	• Apixaban tablets may be crushed and suspended in water/juice or mixed with puree and immediately administered orally. Apixaban may also be given through gastric tubes. • Rivaroxaban can be crushed and mixed with water/puree immediately prior to oral administration. The dose should be immediately followed by food. Rivaroxaban may also be given through gastric tubes. • Edoxaban may be given through gastric tubes. • Most brands of warfarin tablets will disperse in water within 5 minutes if shaken; the resulting dispersion flushes easily via a fine bore feeding tube without blockage.
Concerns with medication adherence / concordance	Warfarin	Patients with poor adherence may be at greater risk of thromboembolic complications with DOACs. DOAC have short half-lives and so missed doses may have greater loss of anticoagulation than warfarin. In general, consideration should be given to the risks and benefits associated with any anticoagulation and individualised patient decision made where there are safety concerns.
Weight greater than 120kg or BMI over 40 kg/m^2	Warfarin	There are limited clinical data available for DOACs in patients at the extreme of weight, and the available pharmacokinetic/ pharmacodynamic evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about under-dosing. Warfarin should be considered first line as there is more evidence and monitoring for therapeutic effect can be carried out. However, if warfarin is deemed unsuitable, careful consideration can be given to the use of a DOAC for patients up to 150kg. Beyond 150kg,

		extreme caution should be applied. A thorough consultation should be carried out by the prescriber with the patient to guide them about the possible treatment options and potential risks and uncertainties around using a DOAC. This should be clearly documented in their medical record. See MIL Vol. 8, No. 5: Atrial Fibrillation and Anticoagulation Management.
Patients who have undergone bariatric surgery or bowel resection, or have malabsorption	Warfarin	Absorption of a DOAC may be affected depending on several factors including site and type of surgery or disease, gastric pH and gut motility. Therefore, warfarin is recommended as this can be monitored and adjusted accordingly. If a DOAC is being considered, please discuss with Haematology (bleep 5529).

Discussion with patient

For patients who lack capacity, a decision should be taken in the patients best interests in line with GMC guidance.

The discussion should cover:

- Stroke and bleeding risk (CHA_2DS_2VASc and HAS-BLED scores)
- Suitable anticoagulation options and the differences between them
  - Dosing
  - Monitoring
  - The effects of other medications, food and alcohol
- How to use anticoagulants
  - The correct dose
  - What to do in case of a missed dose
- Duration of anticoagulation treatment
- Possible side effects and what to do if these occur
- Women of childbearing potential who are taking anticoagulants should be advised to take contraceptive precautions and contact their GP urgently if they think they may be pregnant.
- Rivaroxaban must be taken with food to ensure full absorption
- Dabigatran should be taken with food to reduce the likelihood of heartburn/indigestion

Provide written information covering:

- How anticoagulation may affect dental treatment
- How anticoagulants may affect activities such as sports and travel
- When and how to seek medical help

Medicine information booklets:

- Warfarin – NPSA “yellow book”

  Booklets and patient alert cards can be ordered the Primary Care Support England (PCSE) supply system. Patients will be supplied with a copy of this booklet a personalised alert card if under the Oxfordshire Anticoagulation Service

- Apixaban (Eliquis®)

  Booklets and patient alert cards can be ordered from Bristol-Myers Squibb Medical Information (Telephone: 0800 731 1736; E-mail: medical.information@bms.com)
  Booklets can be downloaded and printed from https://www.eliquis.co.uk/patient/atrial-fibrillation/patient-information-booklet

- Dabigatran (Pradaxa®)

  Booklets and patient alert cards can be ordered from Boehringer Ingelheim Medical Information (Telephone: 01344742579, E-mail: medinfo@bra.boehringer-ingelheim.com). Booklets can be downloaded and printed from https://www.pradaxa.co.uk/assets/patients-support/materials/downloads/spaf-patient-support-booklet.pdf

- Edoxaban (Lixiana®)

  Booklets and patient alert cards can be ordered from Daiichi Sankyo Medical Information (Telephone: 01748828818, E-mail: medinfo@daiichi-sankyo.co.uk)
  Booklets can be downloaded and printed from https://lixiana-hcp.co.uk/documents/lixiana_patient_material_english_2019.pdf

- Rivaroxaban (Xarelto®)

  Booklets and patient alert cards can be ordered from Bayer plc Medical Information (Telephone: 01653563116, E-mail: Medical.information@bayer.co.uk)
  Booklets and alert cards can be downloaded and printed from http://www.xarelto-info.co.uk/hcp/

Prescribing the selected anticoagulant

Please see table 3 below for prescribing information on each DOAC.

Drug Interactions

All four DOACs are substrates for the P-glycoprotein transporter. Additionally, both rivaroxaban and apixaban are metabolised via the cytochrome P4503A4 system. Edoxaban is only minimally eliminated via P4503A4. Table 3 below details many of the currently known interactions. Notably, concurrent use of antiplatelets, steroids and non-steroidal anti-inflammatories significantly increases the patient's risk of bleeding and combined use requires very careful consideration of the risks and benefits including use of a PPI. The following provides some guidance on antiplatelets and anticoagulants:

- Stable coronary artery disease patients (more than 12 months away from ACS, NSTEMI, STEMI, CABG or stent): If warfarin, rivaroxaban apixaban or edoxaban is started, antiplatelet therapy can be stopped, unless high risk of future coronary events (prior stenting of the left main, proximal left anterior descending, proximal bifurcation, recurrent MIs), in which case Cardiology advice should be sought. Until more data are available we would caution against the use of dabigatran in this setting.
- Anyone who develops an ACS or undergoes coronary intervention whilst on an oral anticoagulant for AF, or is diagnosed with AF within 12 months of a coronary event or procedure, should have their antiplatelet and anticoagulant regimen discussed with the relevant interventional cardiologist.

Ongoing monitoring of anticoagulation

Ensure that patients who are taking a DOAC (and their carer where applicable) are clear on the follow-up requirements for anticoagulation therapy. Patients should return on a regular basis for on-going review of their treatment, but as a minimum annually.

At each visit;

- Assess adherence and reinforce advice regarding regular dosing schedule, consider compliance aids if appropriate.
- Enquire about adverse effects such as bleeding.
- Assess for the presence of thromboembolic events
- Enquire about other medicines, including OTC medicines especially aspirin and NSAIDs
- Consider other side effects and carefully assess relation with DOAC, decide for continuation (and motivate), temporary cessation or change of anticoagulant drug

Blood sampling;

- Monitor haemoglobin, renal and liver function yearly
- Renal function should be assessed more frequently (6 monthly) in compromised patients such as the elderly (≥ 75-80 years) or frail (defined as ≥ 3 of the following criteria/; unintentional weight loss, self-reported exhaustion, weakness assessed by handgrip test, slow walking speed/gait apraxia, low physical activity)
- If CrCl ≤ 60 ml/min, recheck patient's renal function at an interval of 'CrCl/10' monthly
- Recheck renal or liver function if there is an inter-current condition that may impact renal or hepatic function.

For dosage in renal impairment see table 3 below.

Missed dose

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 intake as before. If the next dose is due a double dose can be taken. For DOACs with once daily dosing regimen, the forgotten dose can be taken up until 12 hours prior to the next scheduled dose, and then continued on the following day with once a day dosing. For once a day dosing regimens the dose should **not** be doubled within the same day to make up for a missed dose. See SPC for more information on individual drugs.

Overdose

Depending on the amount of suspected overdose, hospitalisation for monitoring or urgent measures is advised.

Table 2. Switching between anticoagulants

When switching between different anticoagulants, it is important to safeguard the continuation of anticoagulant therapy while minimizing the risk of bleeding.

Drug	Switching from warfarin to a DOAC	Switching from DOAC to warfarin	Switching from one DOAC to another DOAC	Switching between a parental anticoagulant and a DOAC
Apixaban	Stop warfarin. Apixaban should be started once INR <2	Commence warfarin at normal initiation dose. Give apixaban and warfarin together for 2 days then check INR before next scheduled dose of apixaban. Dose warfarin as per INR. Continue concomitant treatment until INR≥2 with daily INR check prior to administration of apixaban with dosing of warfarin as per result. Once the INR is in the target range stop treatment with apixaban.	The alternative DOAC can be initiated when the next dose is due. Patients must not be on more than one drug at once.	Start new drug when dose of previous drug would have been due. Patients must not be on more than one drug at once.
Dabigatran	Stop warfarin. Dabigatran should be started once INR <2	CrCl 50ml/min or more, give warfarin and dabigatran together for 3 days before stopping dabigatran. CrCl 30 to 49ml/min give warfarin and dabigatran together for 2 days before stopping dabigatran. In both cases check INR 2 days after stopping dabigatran and dose warfarin accordingly.		
Rivaroxaban	Stop warfarin. Rivaroxaban should be started as follows: • For prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation: INR ≤ 3 • For patients treated for DVT, PE and prevention of recurrence: INR ≤ 2.5	Commence warfarin at normal initiation dose. Give rivaroxaban and warfarin together for 2 days then check INR immediately before next scheduled dose of rivaroxaban. Dose warfarin as per INR. Continue concomitant treatment until INR≥ 2 with daily INR check prior to administration of rivaroxaban with dosing of warfarin as per result. Once the INR is in the target range stop treatment with rivaroxaban.		
Edoxaban	Stop warfarin. Edoxaban should be started once INR ≤ 2.5	Prior to starting the warfarin, reduce edoxaban dose; for patients on 60mg daily reduce to 30mg daily and for patients on 30mg daily reduce to 15mg daily. Co-administer edoxaban and warfarin until INR≥ 2, for up to a maximum of 14 days. During this time of combined therapy, check INR a minimum of 3 times and immediately prior to the dose of edoxaban.		

Table 3. Summary of DOACs for prevention of stroke and systemic embolism in AF

	APIXABAN (ELIQUIS®)	DABIGATRAN (PRADAXA®)	EDOXABAN (LIXIANA®)	RIVAROXABAN (XARELTO®)
Mechanism of action	Direct factor Xa inhibitor	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Criteria for use in non-valvular AF	Presence of one or more of the following risk factors: - Prior stroke or transient ischaemic attack - Age 75 years or older - Hypertension - Diabetes mellitus - Symptomatic heart failure (NYHA Class 2 or above)	Presence of one or more of the following risk factors: - Previous stroke, transient ischemic attack or systemic embolism - Left ventricular ejection fraction less than 40 % - Symptomatic heart failure (NYHA Class 2 or above) - Age 75 years or older - Age 65-74 years with one of the following: diabetes mellitus, coronary artery disease or hypertension	Presence of one or more of the following risk factors: - Congestive heart failure - Hypertension - Age 75 years or older - Diabetes mellitus - Prior stroke or transient ischaemic attack	Presence of one or more of the following risk factors: - Congestive heart failure - Hypertension - Age 75 years or older - Diabetes mellitus - Prior stroke or transient ischaemic attack
Standard Dose	5mg bd	150mg bd (with food)	60mg od	20mg od (with food)
Reduced Dose	2.5mg bd if **2 or more** of the following present: age 80 years or older, body weight 60 kg or less or serum creatinine 133 micromol/L or greater OR 2.5mg bd where CrCl 15-29ml/min*	110mg bd age 80 years or older or concomitant use of verapamil. *Consider* dose reduction from 150mg bd to 110mg bd in the following: age 75-80 years, moderate renal impairment (CrCl 30-50ml/min*), patients with gastritis, oesophagitis or gastroesophageal reflux and other patients at increased risk of bleeding	30mg od if 1 or more of the following present: body weight 60kg or less, CrCl 15-50ml/min* or concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole	15mg od where CrCl 15-49ml/min*
Renal impairment	Do not use if CrCl <15ml/min* Use with caution if CrCl 15-29ml/min*	Do not use if CrCl less than 30ml/min* Consider dose reduction if CrCl 30-50ml/min*	Do not use if CrCl less than 15ml/min* Use with caution if CrCl 15-29ml/min*	Do not use if CrCl less than 15ml/min* Use with caution if CrCl 15-29ml/min*
Hepatic impairment	No data on using in patients with ALT or AST more than twice ULN 2 or total bilirubin greater or equal to 1.5 times ULN – advise avoiding	No data on using in patients with liver enzymes more than twice ULN 2 – advise avoiding	No data on using in patients with ALT or AST more than twice ULN 2 or total bilirubin greater or equal to 1.5 times ULN 2 – advise avoiding	Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
Contraindications (List not exhaustive–refer to current SPC www.medicines.org.uk)	• Hypersensitivity • A lesion or condition, if considered a significant risk factor for major bleeding • Active bleeding • Hepatic disease or impairment • Anticoagulant in use (except during switching -see table 2) • Prosthetic heart valves • Mod-severe mitral stenosis • Pregnancy and breast feeding	• Hypersensitivity • A lesion or condition, if considered a significant risk factor for major bleeding • Active bleeding • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • Anticoagulant in use (except during switching - see table 2) • Prosthetic heart valves • Mod-severe mitral stenosis • Pregnancy and breast feeding	• Hypersensitivity • A lesion or condition, if considered a • significant risk factor for major bleeding • Active clinically significant bleeding • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • Anticoagulant in use (except during switching - see table 2) • Prosthetic heart valves • Mod-severe mitral stenosis • Pregnancy and breast feeding	• Hypersensitivity • A lesion or condition, if considered a significant risk factor for major bleeding • Active bleeding • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • Anticoagulant in use (except during switching - see table 2) • Mod-severe mitral stenosis • Prosthetic heart valvesPregnancy and breast feeding

	APIXABAN (ELIQUIS®)	DABIGATRAN (PRADAXA®)	EDOXABAN (LIXIANA®)	RIVAROXABAN (XARELTO®)
Drug interactions (List not exhaustive–refer to current SPC www.medicines.org.uk)	Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole and posaconazole, rifampicin, carbamazepine, phenytoin, phenobarbital, primidone, St John's Wort. Caution with erythromycin and clarithromycin, diltiazem and amiodarone.	Avoid with HIV protease inhibitors, rifampicin, carbamazepine, phenytoin, phenobarbital, primidone, St John's Wort, dronedarone, ciclosporin, tacrolimus, ketoconazole, itraconazole, voriconazole and posaconazole. Caution with amiodarone, verapamil, erythromycin and clarithromycin.	No data on co-administration with HIV protease inhibitors. Caution (limited data) with rifampicin, carbamazepine, phenytoin, phenobarbital, primidone, St John's Wort and clarithromycin. Dose reduce with ciclosporin, dronedarone, erythromycin or ketoconazole (see information above).	Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole, posaconazole, dronedarone rifampicin, carbamazepine, phenytoin, phenobarbital, primidone, St John's Wort, Caution with erythromycin and clarithromycin.
Extremes of weight	If <50kg or >100-120kg** then exposure of DOAC is variable by 20-30%. It is recommended that the Cockcroft and Gault formula is used to calculate CrCl rather than eGFR.			
Pharmaceutical issues	May be dispersed in water. Stable in dosette boxes.	Capsules can only be stored in original packaging thus not suitable for dosette boxes	May be dispersed in water. Stable in dosette boxes.	May be dispersed in water. Stable in dosette boxes

NB: *Warfarin is the preferred option in those with a creatinine clearance below 30ml/min because of a lack of outcome data for DOACs in this setting. Seek specialist advice in severe renal impairment.
** Warfarin is the preferred option in patients with a weight of more than 120kg or BMI over 40 kg/m^2 due to concerns about under-dosing. See table 1 for further information.
ULN = upper limit of normal

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