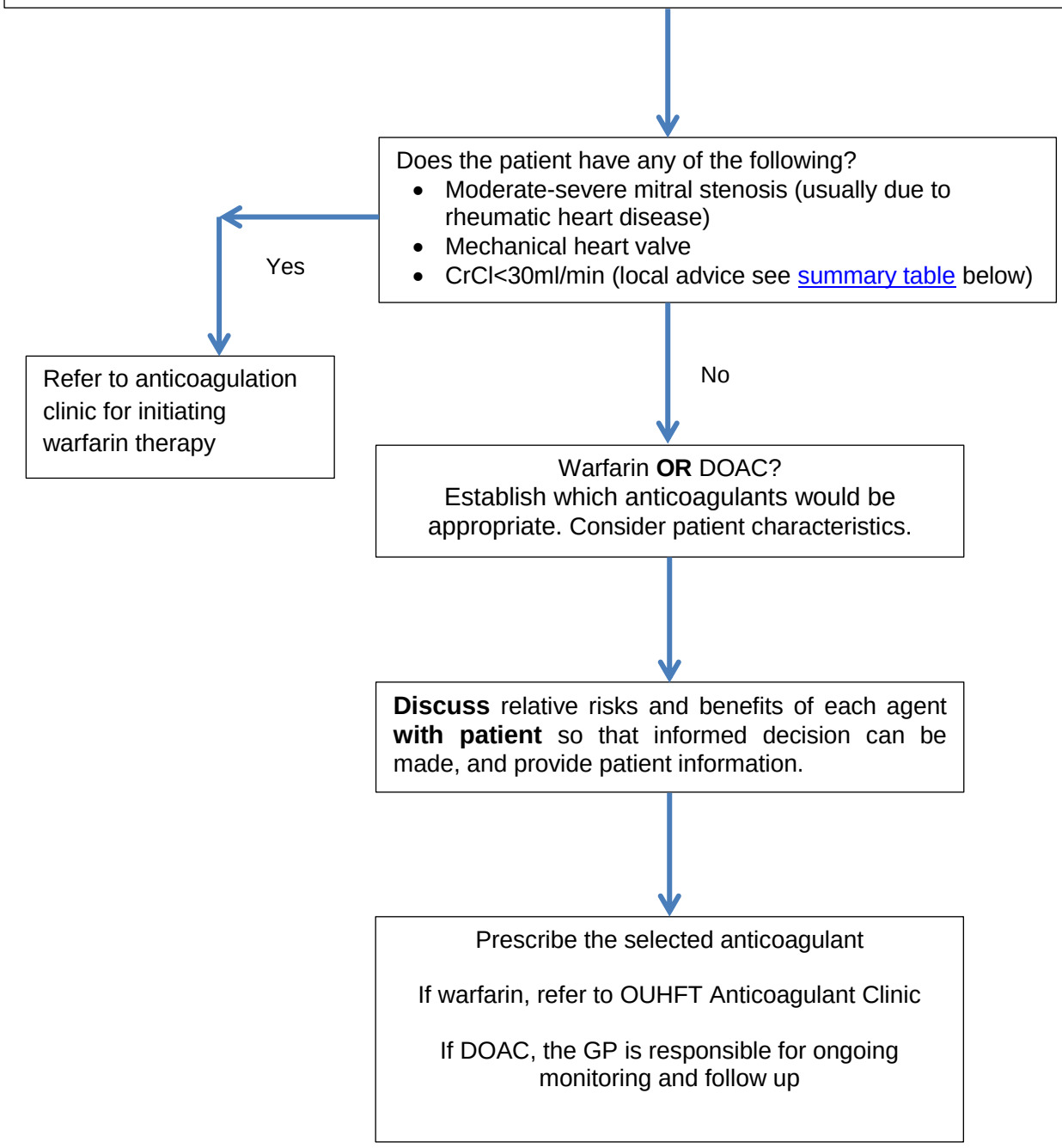
NHS
Oxfordshire
Clinical Commissioning Group

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 anticoagulation clinic for patients initiated on warfarin. Community pharmacists can provide education under the New Medicine Service.



Choice of anticoagulant therapy

The decision about whether to start treatment with warfarin or a DOAC (formerly NOAC) should be made after an informed discussion between the prescriber and the patient about the relative risks and benefits of each agent.

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, poor compliance, failure to comply with monitoring arrangements etc.

Key points for warfarin

- Has been prescribed for more than 50 years.
- Warfarin activity/effect can be measured by an INR and may help give an indication to compliance.
- 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 IHD, ACS or stents follow Cardiology advice regarding use of antiplatelets.

Key points for DOACs

- Compared to warfarin DOACs are relatively new to market.
- No requirement for INR monitoring.
- Compared with warfarin all have a reduced risk of intracranial haemorrhage.
- Idarucizumab is licensed and NICE-approved for dabigatran reversal in adult patients when rapid reversal of its anticoagulant effects is required. There is currently no licensed antidote in the reversal of anticoagulant effect of rivaroxaban, apixaban and 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.
- Useful for patients who have difficulty getting INR measured. Minimum of U&E and LFT annually. Renal function should be assessed and monitored using Cockcroft and Gault formula – Creatinine Clearance (CrCl), especially in patients with extreme BMI.
- 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.

- DOACs have short half-life and so missed doses will have greater loss of anticoagulation than warfarin.
- For patients with IHD, ACS or stents follow Cardiology advice regarding use of antiplatelets.

Patient groups considered to benefit from warfarin include:

- Patients with a history of poor compliance with medication which cannot be improved in the foreseeable future. Serious consideration should be given to whether these patients are suitable for any oral anticoagulation and whether supervised administration of low molecular weight heparin (LMWH) is preferable.
- Patients with a weight of more than 120 kg.
- Contraindications to DOACs:
    - Severe renal impairment (dabigatran CrCl <30 mL/min, rivaroxaban, apixaban and edoxaban CrCl <15 mL/min).
    - Hepatic impairment (elevated liver enzymes >2 x ULN).
    - Interacting drugs with DOACs.
    - Intolerance or depending on the severity of reaction an allergy to a previous DOAC.
- 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 on warfarin despite good compliance.
- 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 such as antibiotics.
- Those with monitored dosage systems (MDS) (an exception is dabigatran as this 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 of considerations when deciding which DOAC 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 compared to warfarin.
Dyspepsia	Apixaban Rivaroxaban Warfarin Edoxaban	Dyspepsia was occurs in 10% of patients on dabigatran
High risk of ischaemic stroke and age < 80 years	Dabigatran 150mg	Dabigatran 150mg bd is the only DOAC shown to be superior to warfarin in reducing ischaemic stroke
Renal impairment – CrCl <30ml/min	Warfarin	DOACs not recommended. Apixaban is the least renally cleared. See summary table below for more detail.
Liver impairment – AST/ALT >2 x ULN	Warfarin	Warfarin is preferred. See summary table below for more detail.
Once a day formulation preferred	Edoxaban Rivaroxaban Warfarin	Rivaroxaban and edoxaban are both once a day administration
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 or apple juice or mixed with apple puree and immediately administered orally. Apixaban may also be given through gastric tubes. • Rivaroxaban can be crushed and mixed with water or apple puree immediately prior to oral administration. The dose should be immediately followed by food. Rivaroxaban may also 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 compliance may be at greater risk of thromboembolic complications with DOACs. DOAC have short half-life and so missed doses may have greater loss of anticoagulation than warfarin.
Weight > 120 kg	Warfarin	Although the Summary of Product Characteristics (SPCs) does not have an upper limit for body weight, OUHFT recommend that DOACs should not be used in patients with a weight of more than 120kg. This is because there are limited clinical data available for 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. See MIL Vol. 8, No. 5: Atrial Fibrillation and Anticoagulation Management.

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
- 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

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
- 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

Patient information resources:

NICE AF patient decision aid summarises information on the topics people with atrial fibrillation most often want to think about and discuss with their healthcare team when deciding on which anticoagulant treatment option to take. The person making this decision can then weigh up the possible advantages and disadvantages of the different treatment options.

Drug information booklets:

- Warfarin – NPSA "yellow book"
  - Booklets and patient alert cards can be ordered the Primary Care Support England (PCSE) supply system
- 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)
- Dabigatran (Pradaxa®)
  - Booklets and patient alert cards can be ordered from Boehringer Ingelheim Medical Information (Telephone: 01344742579, E-mail: medinfo@bra.boehringer-ingelheim.com)
- Edoxaban (Lixiana®)
  - Booklets and patient alert cards can be ordered from Daiichi Sankyo Medical Information (Telephone: 01748828818, E-mail: medinfo@daiichi-sankyo.co.uk)
- 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 summary table 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. The summary table below details many of the currently known interactions. Notably, concurrent use of antiplatelets 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. 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 caretakers 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 as per NICE CG180.

At each visit;

- Assess compliance 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 the summary table 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.

Overdose

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

Switching between anticoagulant regimens

When switching between different anticoagulant regimens, 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.		

Summary table 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 micromole/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	Not recommended in severe hepatic impairment as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy	Not recommended in patients with elevated liver enzymes >2 upper limit of normal. Contraindicated in patients with hepatic impairment or liver disease expected to impact on survival.	Not recommended in severe hepatic impairment as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy	Use with caution as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy
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 below) • Prosthetic heart valves • 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 below) • Prosthetic heart valves • 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 below) • Prosthetic heart valves • 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 below) • Uncontrolled severe hypertension • Prosthetic heart valves Pregnancy and breast feeding
Extremes of BMI	If <50kg or >100-120kg** then exposure of DOAC is variable by 20-30%. It is recommended that at these body weights the Cockcroft and Gault formula is used to calculate CrCl rather than eGFR.			

	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. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort, erythromycin and clarithromycin.	Avoid with HIV protease inhibitors, rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort, dronedarone, ciclosporin, tacrolimus, ketoconazole, itraconazole, voriconazole and posaconazole. Caution with amiodarone, verapamil, erythromycin and clarithromycin.	No data on co-administration with HIV protease inhibitors. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort and clarithromycin. Dose reduce with ciclosporin, dronedarone, erythromycin or Ketoconazole (see information above).	Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole, posaconazole and dronedarone. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's ort, erythromycin and clarithromycin.
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	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 due to concerns about under-dosing.

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