Central and North West London NHS
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Milton Keynes Community Health Services

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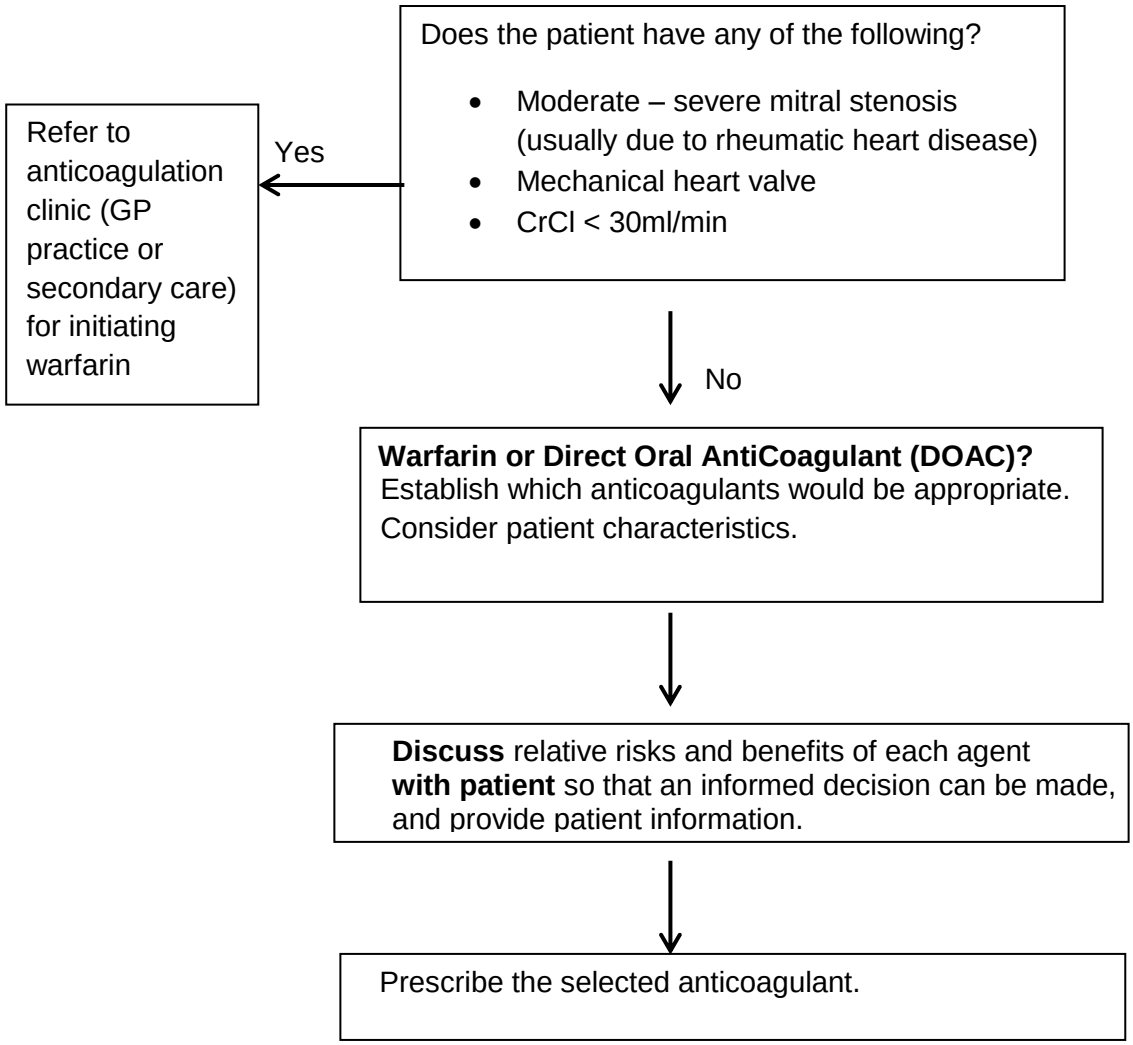
Advice to Prescribers
Decision Support for Anticoagulants

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. This document supports prescribers to choose a suitable anticoagulant once the decision has been made to anticoagulate the patient.

Decision aids may be accessed from:
https://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-update-patient-decision-aid-243734797
and
https://www.anticoagulation-dst.co.uk/

Please note that patients on any type of anticoagulant will need education about their individual anticoagulant and the importance of good compliance. http://www.patient.co.uk/health/anticoagulants



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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 of 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 antiplatelet agents.

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 although some are in development to reverse the anticoagulant effect of rivaroxaban, apixaban and edoxaban. 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, FBC all 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 antiplatelet agents.
- DOACs have some drug-drug interactions

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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:
- Warfarin is recommended if CrCl <30 mL/min. DOACs are contra-indicated if 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.
- Patients with metallic heart valves
- Those patients with triple antibody positive antiphospholipid syndrome

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.
- Those patients requiring long term anticoagulation for VTE prevention (as have lower maintenance doses available)

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
- 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 and Dabigatran should be taken with food to reduce likelihood of heartburn/indigestion.

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Prescribing the selected anticoagulant

Please see summary table below for prescribing information on each DOAC. NB Dabigatran is reserved for hospital use only in patients undergoing hip and knee replacement.

For many patients, Edoxaban represents the most cost-effective choice of DOAC but please take the following into account when selecting a DOAC.

Patient characteristic	Which anticoagulant?	Rationale
Mechanical valve or moderate to severe mitral stenosis	Warfarin	DOACs are contraindicated
High risk of bleeding or patient's concern about bleeding	Edoxaban Apixaban	Reduced risk of bleeding compared to warfarin with Apixaban and edoxaban
History of GI bleed	Apixaban Warfarin	Higher rates of GI bleeding with rivaroxaban and edoxaban compared to warfarin
Dyspepsia	Edoxaban Apixaban Rivaroxaban Warfarin	Dyspepsia rates higher with dabigatran
High risk of ischaemic stroke and age <80 years	Warfarin	Only dabigatran 150mg BD has been shown to be superior to warfarin
Renal impairment • CrCl < 30ml/min • CrCl >30 but <50ml/min	Warfarin Apixaban	Apixaban is least renally cleared.
Liver impairment AST/ALT >2 x ULN	Warfarin	
Triple antibody positive antiphospholipid syndrome	Warfarin	Studies have shown warfarin is superior in this situation. For other forms of antiphospholipid syndrome evidence still lacking. Needs discussion with specialist. Warfarin still viewed as better in many situations
Patient being treated for long term VTE prophylaxis (low risk)	Apixaban Rivaroxaban	Both have lower maintenance doses which are effective at preventing VTE and have more favourable bleeding profiles (apixaban similar to placebo, rivaroxaban similar to aspirin)
Once a day formulation	Edoxaban Rivaroxaban Warfarin	May aid compliance and for those patients requiring help from carers.
Requirement for compliance aid	Edoxaban Apixaban Rivaroxaban	Dabigatran cannot be stored in a dosette box Warfarin should not normally be put in a dosette box unless there is a management plan to cope with dose adjustments
Swallowing difficulties or administration through gastric tube	Apixaban Rivaroxaban Warfarin	Apixaban tablets may be crushed and suspended in water or apple juice or mixed with apple puree and administered immediately. Apixaban may be administered through a gastric tube. Rivaroxaban can be crushed and mixed with water or apple puree and administered immediately. Rivaroxaban may be administered through a gastric tube. Most brands of warfarin will disperse in water within 5 mins if shaken. The resulting dispersion flushes easily via a fine bore feeding tube.
Concerns with medication adherence	Warfarin	Patients with poor compliance may be at greater risk of thromboembolic complications with DOACs. DOACs have a short half-life and so missed doses may have a greater loss of anticoagulation than warfarin.
Weight > 120kg	Warfarin	There is limited clinical information on the use of DOACs and concerns about risk of under dosing.

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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. This should be in discussion with the patient's preferred community pharmacist.
- 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 6 months or sooner
- Recheck renal or liver function if there is an inter-current condition that may impact renal or hepatic function.

Important cautions: Surgery and invasive procedures

Patients on DOACs who undergo surgery or invasive procedures are at increased risk for bleeding. DOACs usually require stopping 24-48 hours prior to the procedure but this depends on the patient's renal function and procedure being done – Specialists to advise GP.

If surgery cannot be delayed the case should be discussed with haematology for advice on reversal if required. Patients on warfarin will have received advice at their pre-op assessment clinic.

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Drug Interactions Summary (to be read in conjunction with the SPC and BNF)

	Edoxaban	Apixaban	Rivaroxaban	Dabigatran
Drug interactions (List not exhaustive–refer to current SPC www.medicines.org.uk)	No data on co-administration with HIV protease inhibitors. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort and clarithromycin. Dose reduce with ciclosporin, dronedarone, erythromycin or Ketoconazole	Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole and posaconazole. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort, erythromycin clarithromycin.	Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole, posaconazole and dronedarone. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort, erythromycin clarithromycin.	Avoid with HIV protease inhibitors, rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort, dronedarone, ciclosporin, tacrolimus, ketoconazole, itraconazole, voriconazole posaconazole. Caution with amiodarone, verapamil, erythromycin clarithromycin.

Please be aware that some GP and Community Pharmacy Systems may classify an interaction between clarithromycin and NOACs as significant risk. However the individual Summaries of Product Characteristics state:

Edoxaban: not mentioned as an interaction but flags on SystmOne as moderate risk

Rivaroxaban: the interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. Flags on SystmOne as moderate risk.

Apixaban: not clinically significant. Flags on SystmOne as significant risk.

Dabigatran: Caution - Concomitant administration of strong P-gp inhibitors (such as amiodarone, verapamil, quinidine, ketoconazole and clarithromycin) is expected to result in increased dabigatran plasma concentrations and potential increase in bleeding risk. Flags on SystmOne as significant risk.

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10. Summary of product characteristics for Rivaroxaban (Xarelto®). Accessed via www.medicines.org.uk.

11. Summary of product characteristics for Dabigatran (Pradaxa®). Accessed via www.medicines.org.uk.

12. Summary of product characteristics for Edoxaban (Lixiana®). Accessed via www.medicines.org.uk.

13. Handbook of Drug Administration via Enteral Feeding Tubes. Accessed via www.medicinescomplete.com.

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)

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) or downloaded and printed from http://www.xarelto-info.co.uk/hcp/

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