Guidance for the safe switching of warfarin to direct oral anticoagulants (DOACs) for patients with non-valvular AF and venous thromboembolism (DVT / PE) during the coronavirus pandemic

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Guidance for the Safe Switching of Warfarin to Direct Oral Anticoagulants (DOACs) for Patients with Non-Valvular AF and Venous Thromboembolism (DVT / PE)

Switching appropriate patients from warfarin to a DOAC may be considered to avoid regular blood tests for INR monitoring. Whilst DOACs require blood tests to assess renal function throughout treatment– the monitoring is predictable, less rigorous than INR testing with warfarin and is routinely carried out in primary care. Switching from warfarin to a DOAC must be done with careful consideration as not all patients are suitable for a switch to DOAC, and in some cases, specialist advice may be required.

Patients should only be switched from warfarin to a DOAC by clinicians in primary or secondary care with experience in managing anticoagulation.

To protect the supply chain for all patients – take a phased approach over the 12-week cycle of INR monitoring.

Consider prioritising patients with poor control of INR as this cohort will require the most frequent INR checks. Address non-adherence if this an underlying reason for poor INR control.

All DOACs are licensed for the prevention of atrial fibrillation (AF)-related stroke in people with non-valvular AF and for the treatment and secondary prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Is anticoagulation still required?
For example, can anticoagulant therapy be stopped in patients with prior DVT / PE, where the risk of recurrence is now considered low – seek specialist advice if necessary

Is a switch to a DOAC appropriate?
A switch from warfarin to a DOAC **should not** be considered for patients:

- With a prosthetic mechanical valve
- With moderate to severe mitral stenosis
- With antiphospholipid antibody syndrome (APLS)
- Who are pregnant, breastfeeding or planning a pregnancy
- Requiring a higher INR than the standard INR range of 2.0 – 3.0
- With severe renal impairment - Creatinine Clearance (CrCl) < 15ml/min
- With active malignancy/ chemotherapy (unless advised by a specialist)
- Prescribed interacting drugs – check SPCs (links below) for full list
    - Some HIV antiretrovirals and hepatitis antivirals - check with HIV drug interactions website at https://www.hiv-druginteractions.org/
    - Some antiepileptics- phenytoin, carbamazepine, phenobarbitone or rifampicin are likely to reduce DOAC levels so should be discussed with an anticoagulation specialist
- On triple therapy (dual antiplatelet therapy plus warfarin) without discussing with an anticoagulant specialist or cardiologist
- There is little data on DOACs for patients with venous thrombosis at unusual sites (e.g. portal vein thrombosis) and these patients should be discussed with an anticoagulation specialist

When switching to a DOAC, care should be taken to follow the recommendations in the relevant SPC:

- Apixaban (Eliquis®) https://www.medicines.org.uk/emc/product/2878/smpc
- Dabigatran (Pradaxa®) https://www.medicines.org.uk/emc/product/4703/smpc
- Edoxaban (Lixiana®) https://www.medicines.org.uk/emc/product/6905/smpc
- Rivaroxaban (Xarelto®) https://www.medicines.org.uk/emc/product/2793/smpc

Choose DOAC drug and dose according to the therapeutic indication, patient age, actual bodyweight, renal function – calculated Creatinine Clearance (CrCl), drug interactions and patient preference/lifestyle (see table below)

Guidance on DOAC Prescribing for Non-Valvular AF and DVT/PE

DOAC	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
How to change from warfarin	**Stop warfarin**. Start DOAC when **INR ≤2.5** - *See additional guidance overleaf* (from EHRA guidance: https://academic.oup.com/eurheartj/article/39/16/1330/4942493?guestAccessKey=e7e62356-8aa6-472a-aeb1-eb5b58315d49)			
Baseline checks	Renal function (CrCl)- serum creatinine (Cr) and bodyweight, full blood count (FBC), liver function tests (LFTs). Use results from last 3 months if stable. If for AF: CHA_2DS_2VASC and HASBLED scores.			
Dosing in Non-valvular AF *(lifelong unless risk:benefit of anticoagulation therapy changes)*	**Prescribe Apixaban 5mg twice daily** Reduce dose to 2.5mg twice daily if at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133 micromol/l or if exclusive criteria of CrCl 15 - 29 ml/min.	**Prescribe Edoxaban 60mg once daily** Reduce dose to 30mg once daily if: Body weight <61kg, or CrCl< 50ml/min, or co-prescribed with ciclosporin, dronedarone, erythromycin or ketoconazole.	**Prescribe Rivaroxaban 20mg once daily** Reduce dose to 15mg once daily if CrCl< 50mL/min in NVAF patients only.	**Prescribe Dabigatran 150mg twice daily** if aged <75 years, CrCl> 50mL/min, low risk of bleeding (weight <50kg with close clinical surveillance) Reduce dose to 110mg twice daily if aged > 80 years or prescribed verapamil. Consider 110mg twice daily based on individual assessment of thrombotic risk and the risk of bleeding in patients aged between 75 and 80 years or with CrCl <50mL/min or with increased risk of bleeding (including gastritis, oesophagitis, gastro-oesophageal reflux).
Dosing in patients with DVT / PE *(loading doses are not required if patient has been stabilised on warfarin)*	Dose is 5mg twice daily (use with caution if CrCl <30ml/min). Check intended duration of therapy. For long term prevention of recurrence 2.5mg twice daily (after 6 months' treatment dose).	Dosing as above. Check intended duration of therapy.	Dose is 20mg daily (consider 15mg dose if CrCl<50ml/min and bleeding risk outweighs VTE risk). Check intended duration of therapy. For long term prevention of recurrence 10mg daily could be considered.	Dosing as above. Check intended duration of therapy.
Duration of therapy for DVT/PE	For a provoked DVT/PE: 3 months treatment if provoking factors have been addressed. For unprovoked DVT/PE or recurrent DVT/PE: At least 6 months treatment dose followed by prophylaxis dosing as indicated/advised.			
Contraindications	CrCl <15ml/min	CrCl <15ml/min	CrCl <15ml/min	CrCl <30ml/min
Cautions See also individual SPCSs		CrCl >95ml/min	CrCl <30ml/min. Take with or after food (15mg and 20mg doses).	Do not use in a standard medication compliance aids (MCA)
Interactions Check BNF: www.bnf.org SPC: www.medicines.org.uk	Ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir - not recommended (See SPC for full details) Rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort – use with caution. Do not use apixaban with patients on strong enzyme inducers for acute VTE treatment	Rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort – use with caution Ciclosporin, dronedarone, erythromycin, ketoconazole – reduce dose as above. (See BNF and SPC for edoxaban for further information)	Ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir, dronedarone – not recommended (See SPC for full details) Rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort – Should be avoided.	Ketoconazole, ciclosporin, itraconazole, tacrolimus, dronedarone - contraindicated (See SPC for full details) Rifampicin, St John's Wort, carbamazepine, phenytoin –should be avoided. Amiodarone, quinidine, ticagrelor, posaconazole – use with caution. Verapamil (use reduced dose). Antidepressants: SSRIs and SNRIs- increased bleeding risk

Pragmatic Approach to Stopping Warfarin and Starting DOAC in relation to the INR

SPCs recommend different INRs at which to initiate DOACs after stopping warfarin:

Apixaban and Dabigatran: Start when INR < 2
Edoxaban: Start when INR < 2.5
Rivaroxaban: Start when INR < 3

This approach would require repeat INR checks daily until the required INR is achieved.

EHRA guidance gives pragmatic guidance on when to start DOACs after stopping warfarin:

- If INR < 2: Commence DOAC that day
- If INR between 2 and 2.5: Commence DOAC the next day (ideally) or the same day
- If INR between 2.5 and 3: Withhold warfarin for 24-48 hours and then initiate DOAC

https://academic.oup.com/eurheartj/article/39/16/1330/4942493?guestAccessKey=e7e62356-8aa6-472a-aeb1-eb5b58315d49

Suggested process for safe switching from warfarin to a DOAC (Undertake steps remotely where possible)

1. Check clinical system for recent U&Es, LFTs and FBC (within last 3 months)
2. At next INR visit– check INR, record weight, take bloods if not already available or are unstable
3. Calculate creatinine clearance (CrCl)
4. Prescribe DOAC at appropriate dose and advise patient to obtain supplies
5. Advise patient when to stop warfarin in relation to starting DOAC (INR should be < 2.5 when DOAC is started)
6. Provide written instructions and involve family members / carers where possible to minimise the risk of patients taking both warfarin and the DOAC concurrently. Particular care should be taken where patients are using medication compliance aids to minimise the risk of incorrect dosing
7. Provide an up-to-date Anticoagulant Alert card
8. Where the switch to a DOAC is undertaken outside the GP practice, provide accurate information relating to indication, baseline tests and monitoring requirements to allow primary care to safely take over prescribing responsibility.
9. Inform community nursing teams if they have been monitoring INR or administering warfarin

Ensure local community pharmacies are made aware of the likely increase in the usage of DOACs locally

Counselling*:* See attached checklist

Monitoring

At least annual review of renal profile if CrCl > 60ml/min with FBC and LFTs

- 6 monthly review if CrCl 30-60ml/min and/or aged >75 years and/or frail
- 3 monthly review of renal profile if CrCl 15-30ml/min

Check for side effects/bleeding issues and patient adherence to therapy at each routine appointment.

For patients in whom DOACs are not suitable – is low molecular weight heparin (LMWH) an option?

- Whenever possible, patients with mechanical heart valves should remain on warfarin, however if monitoring is impossible then a brief period of LMWH could be considered if the patient can be taught to self-inject or a family member that lives with them can administer the injection.
- For other patients in whom DOACs are not an option, consider a LMWH if the patient can be taught to self-inject or a family member that lives with them can administer the injection.

In view of recognised supply issues with LMWH, these should only be used if there are no other appropriate options

For patients continuing warfarin therapy - is self-testing of INR with a CoaguChek self-testing meter a possibility?

There are limited supplies of Coaguchek self-testing meters available in the UK but, where available, these should be used for appropriate patients continuing warfarin therapy. Dosing recommendations should be provided by the patient's current anticoagulation service provider by phone or electronically. See https://www.nice.org.uk/guidance/dg14

DOAC Counselling Checklist

Apixaban (Eliquis®), Dabigatran (Pradaxa®), Edoxaban (Lixiana®), Rivaroxaban (Xarelto®)

DOAC Agent Counselled: ……..……

Counselling points	Sign
Explanation of an anticoagulant (increases clotting time and reduces risk of clot formation) **and explanation of indication for therapy** (AF and stroke risk reduction/DVT/PE)	
Differences between DOAC and warfarin *(if applicable for patients converting from warfarin to DOAC therapy or offering choice of anticoagulation agent)* • No routine INR monitoring • Fixed dosing • No dietary restrictions and alcohol intake permitted (within national guidelines) • Fewer drug interactions	
Name of drug: generic & brand name	
Explanation of dose: strength & frequency	
Duration of therapy: lifelong for AF or explain course length for DVT / PE treatment or prevention	
To take with food (dabigatran and rivaroxaban). Not required for apixaban or edoxaban	
Missed doses: • **Apixaban and dabigatran can** be taken within 6 hours of missed dose, otherwise omit the missed dose • **Edoxaban and rivaroxaban** can be taken within 12 hours of missed dose, otherwise omit the missed dose	
Extra doses taken: obtain advice immediately from pharmacist/GP/NHS Direct (111)	
Importance of adherence: short half-life and associated risk of stroke and/or thrombosis if non-compliant	
Common and serious side-effects and who/when to refer: symptoms of bleeding/unexplained bruising. Avoidance of contact sports. • Single/self-terminating bleeding episode – routine appointment with GP/pharmacist • Prolonged/recurrent/severe bleeding/head injury – A&E Major bleeds managed/reversed by supportive measures, Prothrombin Complex Concentrate (PCC), and availability of antidote	
Drug interactions and concomitant medication: avoid NSAID's. Always check with a pharmacist regarding OTC/herbal/complimentary medicines	
Inform all healthcare professionals of DOAC therapy: GP, nurse, dentist, pharmacist i.e. prior to surgery	
Pregnancy and breastfeeding: potential risk to foetus – obtain medical advice as soon as possible if pregnant/considering pregnancy. Avoid in breastfeeding	
Storage: dabigatran must be kept in original packaging – moisture sensitive. All other DOAC are suitable for standard medication compliance aids/ dosette boxes if required	
Follow-up appointments, blood tests, and repeat prescriptions: where and when	
Issue relevant patient information AF booklet/leaflet and anticoagulant patient alert card	
Give patient opportunity to ask questions and encourage follow up with community pharmacist (NMS – New Medicine Service)	