NHS Grampian

Guidance For Switching Warfarin To DOACs for Adults With Non-Valvular AF And DVT/PE During The COVID-19 Pandemic

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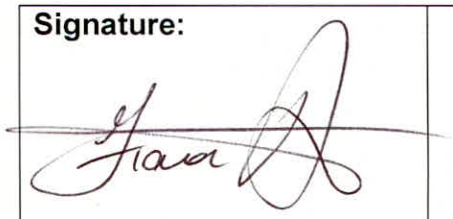		(Refer to Organisational Authorisation, Page -iii-)

Identifier:	Review Date:	Date Approved:
NHSG/COVID19_Warfarin_DOAC/GADTC1081	April 2021	April 2020

Uncontrolled when printed

Version 1

Executive Sign-Off

This document has been endorsed by the Director of Pharmacy and Medicines Management

Signature: 

Title:	Guidance For Switching Warfarin To DOACs for Adults With Non-Valvular AF And DVT/PE During The COVID-19 Pandemic
Unique Identifier:	NHSG/COVID19_Warfarin_DOAC/GADTC1081
Replaces:	N/A – new document
Lead Author/Co-ordinator:	Medicines Management Project Pharmacist
Subject (as per document registration categories):	Guidance
Key word(s):	anticoagulation therapy, warfarin, Direct Oral Anticoagulants, DOAC, non-valvular atrial fibrillation, NVAF, venous thromboembolism, VTE, deep vein thrombosis, DVT, pulmonary embolism, PE, apixaban, Eliquis, dabigatran, Pradaxa, edoxaban, Lixiana, rivaroxaban, Xarelto
Process Document: Policy, Protocol, Procedure or Guideline	Guideline
Document application:	NHS Grampian
Purpose/description:	Guidance For Switching Warfarin To DOACs for Adults With Non-Valvular AF And DVT/PE During The COVID-19 Pandemic.
Group/Individual responsible for this document:	Medicines Management Project Pharmacist/Principal Pharmacist, Medicines Management Team
Policy statement:	It is the responsibility of all staff to ensure that they are working to the most up to date and relevant policies, protocols procedures.

Responsibilities for ensuring registration of this document on the NHS Grampian Information/ Document Silo:

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Physical location of the original of this document:	Pharmacy and Medicines Directorate
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Responsibilities for implementation:

Organisational: Operational Management Team and Chief Executive
Sector General Managers, Medical Leads and Nursing Leads
Departmental: Clinical Leads
Area: Line Manager

Review frequency and date of next review: This guideline will be reviewed in one year or sooner if current treatment recommendations change.

Responsibilities for review of this document:

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Revision History:

Revision Date	Previous Revision Date	Summary of Changes (Descriptive summary of the changes made)	Changes Marked* (Identify page numbers and section heading)
		N/A – New Document	

* Changes marked should detail the section(s) of the document that have been amended, i.e. page number and section heading.

Organisational Authorisations

Document/Guideline authorised by the Grampian Area Drugs and Therapeutics Committee Executive Group

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Guidance For Switching Warfarin To DOACs for Adults With Non-Valvular AF And DVT/PE During The COVID-19 Pandemic

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.

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).

NHS Grampian Formulary choices:
Non-valvular AF (NVAF) – First-line: Edoxaban 60mg; second-line: Apixaban
Venous thromboembolism (DVT/PE) – First-line: Rivaroxaban

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.

Can anticoagulation be stopped in patients with prior DVT / PE?
Therapy should be guided by the anticoagulation duration stipulated at the time of discharge. For a provoked event patients should follow the advice they were given on their finite period of anticoagulation.
For an unprovoked event patients' treatment could be extended to 6 months before being reviewed to reach a final decision on the duration of anticoagulation (long term or not).

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 SmPCs (links below) for full list
  - Some HIV antiretrovirals and hepatitis antivirals - check with HIV drug interactions website at https://www.hiv-druginteractions.org/
  - Some other drugs - 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

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- 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 SmPC:

- 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).

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DOAC	Edoxaban 60mg tablet	Apixaban 2.5mg and 5mg tablets	Rivaroxaban 10mg, 15mg and 20mg tablets	Dabigatran 110mg and 150mg hard capsules
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 6 months if stable.			
Dosing in Non-valvular AF *(lifelong unless risk:benefit of anticoagulation therapy changes)*	**First-line choice for Non-valvular AF** **Prescribe Edoxaban 60mg once daily** Prescribe apixaban if any of the below apply: Body weight ≤ 60kg or CrCl< 50mL/min or > 95mL/min, or co-prescribed with ciclosporin, dronedarone, erythromycin or ketoconazole.	**Second-line choice for Non-valvular AF** **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 ≤ 60kg, or serum creatinine ≥ 133 micromol/l **OR** if CrCl 15 - 29mL/min.	**Third-choice for Non-valvular AF only if edoxaban and apixaban unavailable** **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).
	See NHS Grampian DOAC prescribing guidance for the prevention of stroke and systemic embolism in adults with NVAF for more information, https://foi.nhsgrampian.org/globalassets/foidocument/foi-public-documents1---all-documents/Guide_DOAC.pdf			
Duration of therapy for NVAF	During COVID-19 pandemic establish patients on the treatment dose and review treatment in 6 months.			
Dosing in patients with DVT / PE *(loading doses are not required if patient has been stabilised on warfarin)*	Dosing as above. Check intended duration of therapy.	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).	**First-line choice for VTE (DVT/PE)** 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 and cautions also see individual SmPCs	CrCl < 15mL/min - not recommended. Prescribe apixaban if any of the following: CrCL 15 - 50mL/min or > 95mL/min, or body weight ≤ 60kg; or co-prescribed with P-gp inhibitors.	CrCl <15mL/min - not recommended.	CrCl < 15mL/min - not recommended. CrCl < 30mL/min. Take with or after food (15mg and 20mg doses).	CrCl < 30mL/min – contraindicated Do not use in a standard medication compliance aids (MCA).
Interactions Check BNF: www.bnf.org SmPC: www.medicines.org.uk	Rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort – use with caution. Ciclosporin, dronedarone, erythromycin or ketoconazole – prescribe apixaban. (See BNF and SmPC for edoxaban for further information).	Ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir - not recommended (see SmPC for full details). Co-prescribed with strong enzyme inducers, e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort – use with caution in NVAF; - not recommended for the treatment of DVT/PE.	Ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir, dronedarone – not recommended (see SmPC for full details). Rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort – should be avoided.	Ketoconazole, ciclosporin, itraconazole, tacrolimus, dronedarone – contraindicated (see SmPC 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.

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

SmPCs 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. If it is not possible to perform INR around this time then withhold warfarin for 3 days then start DOAC.

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 6 months).
2. At next INR visit– check INR, record weight, take bloods if not already available or are unstable.
3. Calculate creatinine clearance (CrCl) using Cockcroft-Gault equation (https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation).
4. Prescribe DOAC at appropriate dose (see table above) 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.

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.

This document is a minor adaption of the guidance provided in Williams H *et al*, '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; 26 March 2020'; available at https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Coronavirus/FINAL%20Guidance%20on%20safe%20switching%20of%20warfarin%20to%20DOAC%20COVID-19%20Mar%202020.pdf

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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 and brand name	
Explanation of dose: strength and frequency	
Duration of therapy: anticoagulation 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 24 (call 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 DOACs 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 or practice pharmacy team	

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