Direct Oral Anticoagulants (DOACs)

Joint Guidance for the Humber, Coast and Vale Region

This document has been produced with the agreement and endorsement of Cardiologists, General Practitioners, Pharmacists, ODN, and CCG representatives from the key stakeholder organisations across the Humber, Coast & Vale STP

This document is adapted from the 'Mid Yorkshire NHS Trusts Joint Guidance on DOAC Use' 2018.

1. Introduction

For more than fifty years, vitamin K antagonists such as warfarin have been the only available oral anticoagulants. In recent years, direct oral anticoagulants (DOACs) have gained approval for the treatment and prevention of venous thromboembolism (VTE) and for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). They have similar or better efficacy and safety compared with warfarin and are therefore valuable alternatives[1].

Although warfarin has been shown to be effective for stroke prevention in AF, its use may be limited due to practicalities. Which include: Intense INR monitoring, the need for tight control of anticoagulation, drug and dietary interactions and variable pharmacokinetics.

DOACs have predictable pharmacokinetics, reducing the need for intense monitoring. The DOACs have a rapid onset of action (1-2 hours), a favorable side effect profile and reduced risk of intracerebral haemorrhage in comparison with warfarin. Due to the short half-lives of the DOACs, the anticoagulant effect of DOACs fades rapidly 12–24 hours after the last intake. Strict adherence is crucial. It is therefore important to explain the adverse effects of not being adherent with therapy to the patient (see Appendix 1 for the DOAC counselling patient checklist). DOACs should be used with caution in patients with a calculated creatinine clearance of less than 30ml/min. In patients with a creatinine clearance below 15ml/min, warfarin is the preferred choice in these patients[1].

NICE guidance[2] states that where appropriate, patients should be offered the choice of a DOAC or a vitamin k antagonist. All four DOACs (edoxaban, rivaroxaban, apixaban and dabigatran) are available on all regional formularies. This document is to be used as guidance and should not replace clinical judgment. If the clinician feels one DOAC is more suitable for a particular patient than another; then this should be outlined in the management plan and the DOAC can be used.

2. Aims and scope of guideline

The aim and scope of this guideline is to provide support for clinicians when prescribing a direct oral anticoagulant (DOAC) to patients under their care, after a detailed discussion between the clinician and their patient on the most suitable anticoagulant choice (either vitamin K antagonist or DOAC). **This document is to be used when the choice of treatment is a DOAC**. This document will help to produce standardised prescribing across the Trust and provide safe and effective treatment.

The detailed clinical background for NVAF treatment and VTE diagnosis, and treatment is beyond the scope of this guideline.

3. Implementation and dissemination

The guidance will, following approval by the **Executive Board of the Cardiology ODN,** be disseminated to key stakeholders across the STP geography in written form as a PDF.
From there – ratification will be sought via the appropriate conduit in each organisation; Thrombosis Committee, Drugs and Therapeutics Committee, and Area Prescribing Committee.
Each area will nominate a clinical representative to oversee the process of presentation at the appropriate ratification steps.

4. DOACs and contraindications[3]

Before initiating a patient on a DOAC, ensure there are no contraindications such as:

- Hypersensitivity to the active substance or to any of the excipients
- Active clinically significant bleeding
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Lesion or condition if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulant agent e.g., unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (for more detailed information, please refer to the 'Policy for peri-procedural management of anticoagulation').
- Uncontrolled severe hypertension
- Pregnancy and breast-feeding

5. Practice recommendations: DOACs for stroke prevention

NVAF is defined as AF in the absence of rheumatic mitral stenosis, mechanical or bio-prosthetic heart valve, and mitral valve repair.[2]

Step 1

- Assess CHA_2DS_2-VASc and HAS-BLED scores.
- Offer anticoagulation to men with a CHA2DS2-VASc score of 1.
- Recommend anticoagulation to all patients with a score ≥2.
- Baseline investigations (LFTs, renal function, U&Es, FBC, clotting screen).

Step 2

- Assess which anticoagulation would be most appropriate clinically and discuss with patient to assess their preference.
- Take into account: patients weight, concomitant drug therapy, patient preference, and the following baseline blood results: LFTs, renal function, U&Es and FBC.

Step 3

- Discuss with patient and provide appropriate information on warfarin and DOACs, to allow patient to make informed choice.

Step 4

- Patient to be initiated on warfarin or DOAC (having taken into account clinical situation, contraindications and patient preference). Document clearly in patients medical notes that this has been undertaken.

6. 1 HC&V DOAC preference for stroke prevention in NVAF

DOAC preference for stroke prevention in NVAF is **Edoxaban**

- See tables below for edoxaban dosing
- A particular advantage to using edoxaban is the once daily dosing frequency, which may aid compliance
- Caution is required when using edoxaban with a CrCl<30ml/min- patient will require more frequent monitoring.

Table 1: Edoxaban dosing guide

Recommended dose	60 mg once daily
Dose recommendation for patients with **one or more** of the following clinical factors:	
Body weight ≤ 60Kg	30mg once daily
P-gp Inhibitors (including c*iclosporin, dronedarone, erythromycin, ketoconazole)*	

Renal impairment (from BNF)

Manufacturer advises avoid if creatinine clearance less than 15 mL/minute.

Dose adjustments

Manufacturer advises use a dose of 30 mg once daily if creatinine clearance 15–50 mL/minute

NB: A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin .Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.[4]

6.2 When to switch a person from warfarin to a DOAC[2]

Use the following criteria for patients who are taking warfarin for NVAF and have poor INR control.

Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following:

•Two INR values higher than 5 or one INR value higher than 8 within the past 6 months
•Two INR values less than 1.5 within the past 6 months
•Time in therapeutic range (TTR) less than 65% (warfarin clinic can be contacted to help with this calculation)

Calculate the person's time in therapeutic range (TTR). When calculating TTR:

-Exclude measurements taken during the first 6 weeks of treatment
-Calculate TTR over a maintenance period of at least 6 months

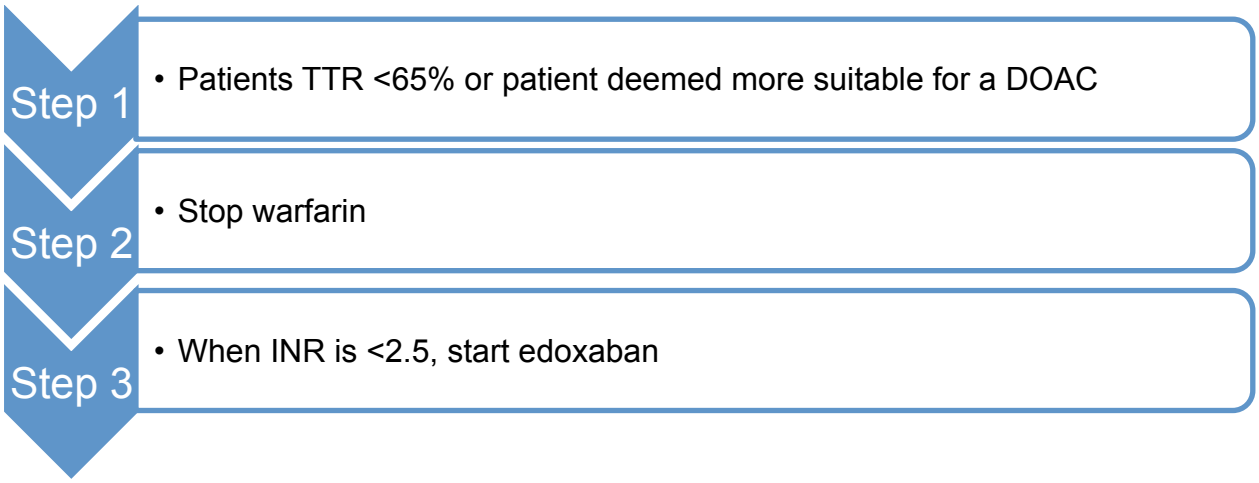
<u>When reassessing anticoagulation, take into account and if possible address the following factors that may contribute to poor anticoagulation control:</u>

-Cognitive function
-Adherence to prescribed therapy
-Illness
-Interacting drug therapy
-Lifestyle factors including diet and alcohol consumption

If poor anticoagulation control cannot be improved, evaluate the risks and benefits of switching to a DOAC and discuss these with the patient.

NB. If a patient is non-adherent to warfarin, do **NOT** prescribe a DOAC. Due to the short half-lives of the DOACs, the anticoagulant effect of DOACs fades rapidly 12–24 hours after the last intake. Strict adherence is crucial.

Fig1 . Summary of switching from warfarin to edoxaban for stroke prevention in NVAF



7. On-going GP monitoring and follow up[5]

Early monitoring (until patient is stabilised)	Long term monitoring	Action if results abnormal
-Monitoring and follow up to be undertaken by the GP -Ideally assess compliance, bleeding, presence of new concomitant medicines and thromboembolic events should be ideally assessed every 6 months (max 12 months).	-If CrCl>60ml/min- U&E's and renal function re-tested annually -If CrCl 36-60ml/min- U&E's and renal function re-tested every 6 months -If CrCl 15-35ml/min- U&E's and renal function re-tested every 3 months -If baseline CrCl <15ml/min, DOAC unsuitable[3]	-**Renal function:** Reduce dose as per manufacturer's guidance. If CrCl <15ml/min, switch to warfarin. **-Liver function (test at least annually):** Elevated liver enzymes (ALT/AST >2x ULN) or total bilirubin >1.5 ULN) consider switching to warfarin. -**Full blood count (test at least annually) :** An unexplained fall in haemoglobin and/or haematocrit may suggest that occult bleeding is occurring and may require further investigations.

Adapted from Sheffield Teaching Hospitals NHS Foundation Trust: 'Anticoagulation for stroke prevention in non-valvular AF: joint primary and secondary care guidance'.

8. References

1) H. Heidbuchel, EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. European Heart Journal, 2013.
2) National institute for health and care excellence (NICE), 2014.*Atrial fibrillation: management*, CG180. London: NICE.
3) Lixiana (edoxaban) 60mg & 30mg film coated tablets, Daiichi Sankyo, last revised July 2017
4) Sheffield Teaching Hospitals NHS Foundation Trust, 'Anticoagulation for stroke prevention in non-valvular atrial fibrillation: joint primary and secondary care guidance', May 2015.

DOAC counselling quick guide for healthcare professionals

- **DOACs work by blocking a substance in the body which is involved in blood clot formation**

1. **Indication** -

DOAC	Licensed indication
Apixaban	DVT, VTE prophylaxis post knee/hip replacement, PE, AF
Rivaroxaban	DVT, VTE prophylaxis post knee/hip replacement, PE, AF, ACS prophylaxis
Edoxaban	DVT, PE , AF
Dabigatran	DVT, VTE prophylaxis post knee/hip replacement, PE, AF, Stroke prophylaxis

2. **Duration –** AF – lifelong**,** Knee replacement – 14 days post-op, Hip replacement -35 days post-op, PE/DVT – 3-6 months usually *(however prescribers decision),* ACS – 12 months usually.
3. **Monitoring –**FBC**,** LFTs, renal function. No INR tests are required. "Your GP will take care of your check-ups concerning blood tests". The frequency of blood tests is dependent on age and renal function.
4. **Administration –** Once daily doses can be taken at any time of the day, however should be the same time each day – *establish the time of day with the patient*. Twice daily doses should be taken morning and night *(12 hourly).*
   Dabigatran capsules should not be crushed, chewed or opened– keep in original box.
5. **Missed doses – *Twice daily dosing*: -** The forgotten dose can be taken up to six hours prior to when the next dose is due. If the next dose is due in less than 6 hours, they should omit the missed dose and take the next scheduled dose as normal.
   Once daily dosing: - The forgotten dose can be taken up to 12 hours after the scheduled intake. If the next dose is due in less than 12 hours, they should omit the missed dose and take the next scheduled dose as normal.
   Compliance *is extremely important – one missed dose can leave the patient without anticoagulation cover due to the short half-life.*
6. **Common interactions**

Drug	Interaction
NSAIDs	Increased bleeding risk
SSRIs	Increased bleeding risk
Clarithromycin	Increase effects of DOAC
Verapamil	Increase effects of DOAC
Amiodarone	Increase effects of DOAC

Alcohol can interact with DOACs and may cause bleeding – it is important to avoid heavy drinking and binge drinking. Moderate drinking within the national limits of 14 units per week is permitted.
(Other interactions – please check BNF or Stockleys)

7. **Common side effects -** Abdominal pain, anaemia, diarrhoea, dyspepsia, nausea
8. **Bleeds risk-** Black tarry stools, fresh blood in urine, nose bleeds, coughing up blood and bruising. Inform GP as soon as possible if any of these occur.
   "If you experience any uncontrollable bleeding or notice signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) consult your doctor immediately".
9. **Lack of reversal agent** – Apart from dabigatran, there are currently no licensed reversal agents available. Things can still be done to help control a bleed if one occurs. Other reversal agents will be locences very soon for each of the DOACS
10. **Other Healthcare professionals –** Importance of making other healthcare professionals aware that they are taking warfarin :-
    - Dentists if you are taking a DOAC before any procedure or check-up.
    - Pharmacists if buying any OTC medicines - *If needing pain relief, paracetamol is safest.*

Adapted from guidance produced by Jinnan Azeez- Rotational Pharmacist (validated by Kirsty Dove – Advanced Clinical Pharmacist- Cardiology and Anticoagulation),Mid Yorkshire Hospitals NHS Trust January 2017

Appendix Equality Impact Assessment

INITIAL ASSESSMENT/SCREENING

An impact assessment is a way of finding out whether an existing or proposed policy affects different groups of people in different ways and whether there is adverse impact on a group.

This form is to be used for new and existing policies and service developments, where a question is not applicable to your assessment, please indicate.

Managers Name	
Policy Title **Direct oral anticoagulants (DOACs) guidance**	
Policy Statement The aim and scope of this guideline is to provide support for clinicians when prescribing a direct oral anticoagulant (DOAC) to patients under their care, after detailed discussion between the clinician and their patient on the most suitable anticoagulant choice (either vitamin K antagonist or DOAC). **This document is to be used when the choice of treatment is a DOAC**. This document will help to produce standardised prescribing across the trust and provide safe and effective treatment. The detailed clinical background for NVAF treatment and VTE diagnosis, and treatment is beyond the scope of this guideline.	
Which groups does the policy benefit Patients who decide a DOAC is their preferred choice of anticoagulation and healthcare professionals who prescribe DOACs.	
Related polices that may be affected by changes -Anticoagulation -Peri-procedural management of oral anticoagulation	
Names of staff and public (if applicable) who participated in the assessment, date of assessment **Indicate either Y or N in each Box below in answer to the following questions/statements** **(cannot be both Y & N in same box or left blank)**	

	Age	Disability	Ethnicity	Religion	Gender/ transgend	Sexual
Do different groups have different needs, experiences, issues and priorities in relation to the policy or service?	Y*	N	N	N	N	N
Is there potential for or evidence that, the policy or service will discriminate against certain groups?	N	N	N	N	N	N
Is there public concern in the policy area about actual, received or potential discrimination against particular groups?	N	N	N	N	N	N
Is there doubt about answers to any of the above questions	N	N	N	N	N	N

If the answer to any of the above is 'yes' an Intermediate assessment in the relevant area(s) is required. If not please complete below and then submitted to the relevant board/committee for approval.

***does not include paediatric patient groups**

Date: 29th April 2019

Clinical lead name: Dr Simon Thackray