Bwrdd Iechyd Prifysgol Abertawe Bro Morgannwg University Health Board

INITIATION & MONITORING OF DIRECT ORAL ANTICOAGULANTS (DOACS)

Background

This guideline is to be used along with the relevant NICE[1] and local decision aides in deciding with the patient the most appropriate anticoagulant for the specific indication, based on the patient's risk of thromboembolic events versus the risk of bleeding. If a decision is made to start a DOAC this guideline will support the appropriate initiation, subsequent maintenance dose and ongoing monitoring of the DOAC.

The focus of this guideline is for the indications of stroke prevention in non-valvular atrial fibrillation (NVAF) and the treatment of venous thromboembolism (VTE). Indications outside of this are not covered and the specific marketing authorisation for each DOAC should be consulted. The monitoring advice in this guideline is a consensus based on the European Society of Cardiology (ESC) guidelines and expert opinion to ensure a consistent approach across the health board. Only licensed indications and doses are included in this guideline, any clarification of choice, dose or monitoring of DOAC should be discussed with a haematologist.

There are four DOACS currently available on the ABMUHB drug formulary that can be prescribed; Apixaban, Dabigatran, Edoxaban and Rivaroxaban.

Initiation

If the indication for anticoagulation is NVAF **then no more than 6 weeks** before initiation of a DOAC the patient's risk of stroke must be assessed and their CHA_2DS_2VASc score documented. Their bleeding risk must also be assessed and documented using the HASBLED tool. The Health board recommends the AWMSG document 'All Wales Risk/Benefit Assessment Tool for Oral Anticoagulation'[2] to record these details.

For all indications **no more than 6 weeks** prior to initiation of a DOAC the following baseline tests must be undertaken and the results reviewed and documented:

- Clotting screen
- Urea and electrolytes
- Liver function
- Full blood count
- Blood pressure
- Body weight

Body Weight: Patients at extremes of body weight have not been included in the main DOAC studies, the current recommendation is that patients who are **<50kg or >120kg** must be discussed with a haematologist on an individual basis before being initiated on a DOAC.

Renal Function: When deciding on an appropriate dose of DOAC, renal function must be calculated using the Cockcroft and Gault equation (see below) **NOT** eGFR.

$$\text{CrCl (ml/min)} = \frac{\mathbf{F} \times (140-\text{age}) \times \text{weight in kg}}{\text{Creatinine in micromol/L}}$$

where **F** =
1.23 (in males)
1.04 (in females)

The equation requires the most recent weight of the patient. The **ACTUAL** weight should be used rather than ideal or adjusted body weights when calculating the creatinine clearance (CrCl) for Rivaroxaban, Apixaban and Edoxaban (**with the exception of Dabigatran, where ideal body weight should be used in overweight patients when there actual body weight is > 120% of their ideal body weight**).

Ideal body weight (IBW):
Male: IBW (kg) = [(height (cm*) – 152.4) x 0.9] + 50
Female: IBW (kg) = [(height (cm*) – 152.4) x 0.9] + 45.5

* Height in inches x 2.54 = Height in cm

There are calculators for creatinine clearance and ideal body weight available online or as an app for example MDCalc available at https://www.mdcalc.com/

Concurrent Medication: consider the potential for drug interaction with the patient's current medication.

The patient must be counselled using the appropriate Health Board checklist for the DOAC and given a completed anticoagulant alert card.

After initiation of the DOAC the patient must be seen within 4 weeks for an initial review[3] and then at least once more within the 6 months following initiation.

During each face-to-face review the following must be checked and documented

1. Adherence (ideally with inspection of medication in addition to appropriate questioning) – any missed doses. Re-educate on importance of strict intake schedule.
2. Thromboembolism - any event that might signal thromboembolism
3. Bleeding
4. Other side effects - report via yellow card if appropriate
5. Co-medications – any change to prescription drugs, over the counter drugs or herbal medicines.
6. Need for blood sampling (see monitoring section below)

Table 1. **DOAC treatment regimens in Non-Valvular Atrial Fibrillation.***

DOAC	Starting & Maintenance Regimen	Reduced Dose Criteria	Reduced Dose	Renal Function Contraindication
Dabigatran	150mg bd	Reduce dose if one or more of the following are present: • Age >80 • Taking Verapamil Consider dose reduction based on thromboembolic and bleeding risk in patients who have one or more of the following: • Age 75-80 • CrCl 30-50ml/min • Gastritis, oesophagitis, GORD	110mg bd	CrCl <30ml/min
Rivaroxaban	20mg od	Reduce dose if: • CrCl <50ml/min	15mg od	CrCl <15ml/min#
Apixaban	5mg bd	Reduce dose if two or more of the following are present: • Serum Cr ≥133 • Age ≥80 • Weight ≤60kg **OR** reduce dose if: • CrCl <30ml/min	2.5mg bd	CrCl <15ml/min#
Edoxaban	60mg od	Reduce dose if one or more of the following are present: • CrCl ≤ 50ml/min • Weight ≤ 60kg • Taking P-gp inhibitors: Ciclosporin, Dronedarone, Erythromycin, Ketoconazole	30mg od	CrCl <15ml/min#

P-gp: P-glycoprotein inhibitor; CrCl: Creatinine Clearance; Serum Cr: Serum Creatinine; GORD: gastro oesophageal reflux disease.

Caution is required when prescribing in patients with CrCl <30ml/min and close monitoring is required. DOACS are licensed in severe renal impairment but DOAC studies excluded this group of patients leading to extrapolated effectiveness and safety outcome data.

*In conjunction with the table the manufacturers SPC should be consulted for a full list of DOAC contraindications, interactions and dosing information. http://www.medicines.org.uk/emc/

Table 2. DOAC treatment regimens in venous thromboembolism*

DOAC	Starting Regimen	Maintenance Regimen	Reduced Dose Criteria	Reduced Dose	Renal Function Contraindication
Dabigatran	Initially 5 days of treatment dose LMWH then Dabigatran 150mg bd	150mg bd	Reduce dose if one or more of the following: • CrCl <50ml/min • Age >80 • Taking Verapamil Consider dose reduction based on thromboembolic and bleeding risk in patients who have one or more of the following: • Age 75-80 • CrCl 30-50ml/min • Gastritis, oesophagitis, GORD	110mg bd	CrCl <30ml/min
Rivaroxaban	15mg bd for 3/52, then maintenance regimen. (Take with Food)	20mg od	Consider reducing **maintenance** dose if perceived bleeding risk is greater than thromboembolic risk and: • CrCl <50ml/min	15mg od	CrCl <15ml/min#
Apixaban	10mg bd for 7 days, then maintenance regimen	5mg bd, reduce to 2.5mg bd after 6 months of treatment	Use with caution if: • CrCl <30ml/min, no dose reduction recommended.	No dose reduction recommended	CrCl <15ml/min#
Edoxaban	Initially 5 days of treatment dose LMWH then Edoxaban 60mg od	60mg od	Reduce dose if one or more of the following: • CrCl ≤ 50ml/min • Weight ≤ 60kg • Taking P-gp inhibitors: Ciclosporin, Dronedarone, Erythromycin, Ketoconazole	30mg od	CrCl <15ml/min#

P-gp: P-glycoprotein inhibitor; CrCl: Creatinine Clearance; Serum Cr: Serum Creatinine; GORD: gastro oesophageal reflux disease.

Caution is required when prescribing in patients with CrCl <30ml/min and close monitoring is required. DOACS are licensed in severe renal impairment but DOAC studies excluded this group of patients leading to extrapolated effectiveness and safety outcome data.

*In conjunction with the table the manufacturers SPC should be consulted for a full list of DOAC contraindications, interactions, dosing information. http://www.medicines.org.uk/emc/

Monitoring

No less than 10 months and no more than 13 months following initiation of a DOAC and thereafter at least on an annual basis, the patient must be reviewed and the findings systematically documented. This must include: appropriateness of continued anti-coagulation; re-assessment of bleeding risk using the HASBLED tool and a full face-to-face medication review.

During each face-to-face review the following must be checked and documented

1. Adherence (ideally with inspection of medication in addition to appropriate questioning) – any missed doses. Re-educate on importance of strict intake schedule.
2. Thromboembolism - any event that might signal thromboembolism
3. Bleeding
4. Other side effects - report via yellow card if appropriate
5. Co-medications – any change to prescription drugs, over the counter drugs or herbal medicines.
6. Need for blood sampling:

DOACS are marketed on their benefit over existing anticoagulation of not requiring any specific monitoring. However, due to their principal route of renal excretion, periodic measurement of renal function is needed depending on the patient's baseline result.

Standard monitoring required includes:

- Renal Function (U&E's)
- Full Blood Count (FBC)
- Liver Function Tests (LFT's)

Below is a table which sets out the frequency of blood monitoring required for DOAC treatment.

More frequent review and monitoring may be required to support compliance, side effects and patients at higher risk of bleeding. Patients at higher risk include:

- the elderly (>75-80 years),
- the 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),
- those where an intercurrent condition may affect renal function

Table 3. DOAC monitoring requirements

DOAC	Baseline Renal Function			FBC	LFT's
	15-29ml/min	30-59ml/min	>60ml/min		
• Rivaroxaban • Apixaban • Edoxaban	3 monthly	6 monthly	12 monthly	12 monthly	12 monthly
• Dabigatran	Contraindicated	6 monthly	12 monthly	12 monthly	12 monthly

At each monitoring review the dose of DOAC must be checked in line with the recommendations in Table 1 and 2 depending on the indication, and adjusted where appropriate.

For advice on the perioperative management of DOACs for elective surgery see the guidelines on coin available at:
http://howis.wales.nhs.uk/sites3/Documents/926/CID69%20Perioperative%20management%20of%20elective%20surgery%20patients%20taking%20warfarin%20DOACS%20or%20antiplatelets..pdf

References

1) NICE Patient Decision Aid available at https://www.nice.org.uk/guidance/cg180/resources/patient-decision-aid-pdf-243734797
2) AWMSG 'All Wales Risk/Benefit Assessment Tool for Oral Anticoagulation available at http://www.awmsg.org/docs/awmsg/medman/Risk-Benefit%20Assessment%20Tool%20for%20Oral%20Anticoagulant%20Treatment%20in%20People%20with%20Atrial%20Fibrillation.pdf
3) Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Heidbuchel et al. EP Europace, Volume 17, Issue 10, 1 October 2015, Pages 1467–1507. Available at https://doi.org/10.1093/europace/euv309

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