Thrombosis and Anticoagulation Clinical Guidelines

INITIATION & MONITORING OF DIRECT ORAL ANTICOAGULANTS (DOACS)

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Section 1: Background

This guideline is to be used along with the relevant NICE 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 SBUHB drug formulary that can be prescribed; Apixaban, Dabigatran, Edoxaban and Rivaroxaban.

This document does not offer guidance on the diagnosis of the above conditions, or guidance on the choice between warfarin or a DOAC (or the choice between specific agents)

For guidance on specific conditions please refer to local and national guidance

Initiation

Confirm Valid Indication

AF

All DOAC's are licensed for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors

The suitability of DOAC's for patients in valvular disease has recently changed. The following is guidance from the EHRA .

Table 1 Selected indications and contraindications for NOAC therapy in AF patients

Condition	Eligibility for NOAC	Comment
Mechanical prosthetic valve	Contraindicated	Excluded from pivotal RCTs Data indicating worse outcome[15,16]
Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	Excluded from pivotal RCTs Little rationale for less efficacy and safety vs. VKA
Other mild to moderate valvular disease (e.g. degenerative aortic stenosis, mitral regurgitation etc.) Bioprosthetic valve/valve repair (after >3 months postoperative)	Included in NOAC trials Acceptable	Data regarding efficacy and safety overall consistent with patients without valvular heart disease[12,17–22] Some data from NOAC RCTs Single RCT indicating non-inferiority to VKA[24] Patients without AF usually on ASA after 3–6 months post-surgery, hence NOAC therapy acceptable for stroke prevention if diagnosed with AF
Severe aortic stenosis	Limited data (excluded in RE-LY)	No pathophysiological rationale for less efficacy and safety Most will undergo intervention
Transcatheter aortic valve implantation	Acceptable	Single RCT + observational data May require combination with APT[25,26]
Percutaneous transluminal aortic valvuloplasty	With caution	No prospective data May require combination with APT
Hypertrophic cardiomyopathy	Acceptable	No rational for less efficacy and safety vs. VKA Observational data positive for NOACs[33–36]

Hatched, limited data; See text for details.
AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized clinical trial; VKA, vitamin K antagonist.

DOAC'S SHOULD NOT BE USED IN PATIENTS WITH MECHANICAL HEART VALVES

VTE

Please refer to the HB

- Deep Vein Thrombosis (DVT) guidelines (CID3576) and Pulmonary Embolism (PE) guidelines (CID2068),
- Cancer Associated Thrombosis (CAT) guidelines (CID2980)

Risk Assessment on initiation	**AF**	Calculate stroke/systemic embolism risk using the **CHA_2DS_2-VASc score** **Current NICE Guidance (NG196) recommend:** - **Offering anticoagulation for those patients with AF and a CHA_2DS_2-VASc score of 2 or above** - **Considering anticoagulation for male patients with AF and a CHA_2DS_2-VASc score of 1 or above** Calculate bleeding risk using the **ORBIT-AF bleeding score.** If clinical systems are yet to be updated to incorporate ORBIT, then continue using **HAS-BLED score.** **The findings of the risk assessment should be documented in an appropriate and accessible format. For patients where the drugs are initiated in one setting but ongoing prescribing is in another, the information on the baseline assessment should be transferred (e.g. via a discharge summary, clinic letter, etc)**
	VTE	Usually undertaken in secondary care
Identify contraindications		➢ Known intolerance to anticoagulation/previous serious bleed (consider a lesion or condition that is a significant risk for major bleeding e.g. current or recent gastrointestinal ulceration, known or suspected oesophageal varices) ➢ Hepatic disease associated with coagulopathy (especially if baseline INR >1.5) ➢ Mechanical heart valve ➢ Transcatheter aortic valve implantation within last 3/12 ➢ Mitral valve replacement or repair within last 3/12 ➢ Known moderate to severe mitral stenosis (valvular AF) ➢ Active or underlying cancer (however recent data for apixaban, rivaroxaban and edoxaban shows that these drugs are safe and effective in most cancer groups, with the exception of those with upper gastrointestinal malignancy or genito-urinary cancers) ➢ Pregnant/breastfeeding or planning a pregnancy

		➢ Triple positive antiphospholipid syndrome (APLS) ➢ AF patients ≥ 75 years old with a stable INR on warfarin (TTR ≥ 70%): A recent study showed worse bleeding outcomes in elderly patients with AF and stable INR control were switched to DOAC's. Consider maintaining warfarin
Obtain Actual Body Weight		Measured within the past 12 months Recruitment of patients weighing <50Kg or >120Kg to the phase III DOAC studies was low ***Low Body Weight*** ➢ **Until further data becomes available, DOAC's should be avoided if possible in patients weighing <50Kg** ***High Body Weight*** ➢ **Patients <120 Kg or BMI < 40 kg/m^2:** Any DOAC may be used (if no other contraindication) ➢ **Patient 120-150 Kg or BMI 40-50 kg/m^2:** Apixaban or rivaroxaban at standard doses ➢ **Patient >150 Kg or BMI >50 kg/m^2:** Apixaban or rivaroxaban may be considered considering risks and benefits of alternative anticoagulants (i.e. warfarin). Consider serum levels **Acute VTE:** Suggest delaying DOAC initiation in high body weight individuals with an acute VTE until outside of the acute phase of treatment (i.e. the first 7 to 30 post VTE diagnosis, dependent on severity of event)

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

<table>
<tr><td rowspan="3">Review other bloods</td><td>Clotting screen</td><td colspan="4">Review with haematology if deranged baseline clotting screen (especially if INR ≥ 1.5)</td></tr>
<tr><td rowspan="2">Liver function</td><td>Apixaban</td><td>Dabigatran</td><td>Edoxaban</td><td>Rivaroxaban</td></tr>
<tr><td>Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk

It is not recommended in patients with severe hepatic impairment

It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) No dose adjustment required

Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin ≥ 1.5 x ULN were excluded in clinical studies. Therefore apixaban should be used cautiously in this population</td><td>Patients with elevated liver enzymes > 2 ULN were excluded in the main trials. No treatment experience is available for this subpopulation of patients, and therefore the use of dabigatran is not recommended in this population. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated</td><td>Edoxaban is not recommended in patients with severe hepatic impairment

Edoxaban should be used with caution in patients with mild or moderate hepatic impairment

Patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN were excluded in clinical studies. Therefore edoxaban should be used with caution in this population).</td><td>Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C</td></tr>
</table>

	Full blood count	**Haemoglobin (Hb):** If Hb low to identify cause prior to initiating in AF patients. Appropriate first line investigations include blood film, reticulocyte count, B12/folate/ferritin to exclude nutritional deficiency, renal and liver chemistries. Beyond that, further specialised investigations are needed In VTE patients this may require discussion with the VTE service **Platelets (PLTS):** Thrombocytopenia is defined as a platelet count < 150 x 109/l Differential diagnosis includes immune peripheral consumption (ITP), any cause of bone marrow failure (aplasia, malignant infiltration, myelodysplasia, B12 / folate deficiency), alcohol, medication, sepsis, hypersplenism, disseminated intravascular coagulation (DIC) and TTP / HUS. - Patients with known ITP should be referred to their haematologist to discuss anticoagulation - The following should be referred urgently for haematology assessment: • Platelet count < 50 x 10^9/l • Platelet count 50 - 80 x 10^9/l in association with: I) other cytopenia (Hb < 10g/dl, Neutrophils < 1 x 10^9/l) or II) splenomegaly, lymphadenopathy, pregnancy, upcoming surgery - Other thrombocytopenia should be investigated as per All-Wales thrombocytopenia pathway - Following appropriate investigations, patients with a stable platelet count of more than or equal to >80 x 10^9/l, can be commenced on anticoagulation
	Blood pressure	Address uncontrolled hypertension- systolic BP >160mmHg increases bleed risk

Identify any potential interactions	Consider the potential for drug interaction with the patient's current medication. Consult the relevant product SmPC for guidance **Concurrent antiplatelet medication** ➢ The decision to concomitantly prescribe antiplatelets with a DOAC should be reviewed on an individual basis ➢ The ESC and EHRA guidelines recommend OAC monotherapy, and not combination therapy with antiplatelets, in AF patients with stable Coronary Artery Disease who have not had an Acute Coronary Syndrome (ACS) and / or coronary intervention / stent in the previous 12 months
Identify the correct dosing	➢ For prescribing DOAC's in Non-Valvular Atrial Fibrillation see page 9 ➢ For prescribing DOAC's in VTE see page 10 Dosing should be as per the SmPC. Recent evidence has shown that inappropriately reduced DOAC dosing in patients with bleeding concerns results in diminished efficacy, with no clear reduction in bleeding risk.
Educate the patient	Healthboard counselling tools are available on COIN for apixaban (VTE or AF), dabigatran (AF) edoxaban (AF), and rivaroxaban (VTE or AF) In addition, booklets may be ordered directly from the manufacturer

Prescribing DOAC's in Non-Valvular Atrial Fibrillation (AF)

In conjunction with the table the manufacturers SPC should be consulted for a full list of DOAC contraindications, interactions, dosing information

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.

Prescribing DOAC's in VTE

***In conjunction with the table the manufacturers SPC should be consulted for a full list of DOAC contraindications, interactions, dosing information.**

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 (can be reduced to 10mg OD after 6 months)	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.

Guidance for switching between warfarin and DOAC's (N.B. See above caution in patients ≥ 75 y/o)			
DOAC	**INR in which a DOAC may be safely initiated in a patient with AF**	**INR in which a DOAC may be safely initiated in a patient with VTE**	**What to do if INR is not in range**
Dabigatran	<2.0	<2.0	**The following is adapted from the EHRA practical guidance 2021** ➢ **If the INR is ≤ 2.0:** *Start the DOAC immediately* ➢ **If the INR is 2-2.5:** *Start the DOAC the next day (ideally) or the same day* ➢ **If the INR 2.5-3:** *Withhold warfarin for 24-48 hours, then start the DOAC* ➢ **If the INR >3:** *Postpone starting the DOAC, calculate how long it would be expected for the INR to fall sufficiently based upon the drug kinetics (48-72hours), and re-check INR. Follow steps above* ▪N.B. There are differences in the pharmacokinetics of VKA's, with accenocoumarol having the shortest half-life, hence the INR would be expected to fall quicker *The above guidance has been designed for patients being anticoagulated for AF. It is worth noting that in patients who are at a high thrombotic risk (e.g. those within 3 months of a diagnosis of a VTE) INR's should not be allowed to go sub therapeutic for prolonged periods. Therefore more regular INR checks would likely be required during the transitional phase*
Rivaroxaban	≤ 3.0	≤ 2.5	
Apixaban	<2.0	<2.0	
Edoxaban	≤ 2.5	≤ 2.5	

Follow up

The first follow up should be within four weeks of initiation

Thromboembolic events	Review for any signs or symptoms that may imply the possibility of a thromboembolic events In the context of DVT, also consider the presence of post-thrombotic syndrome. Further guidance on the management of the condition can be found in the health board guidelines on the diagnosis and management of DVT CID3576
Bleeding	Review for any signs or symptoms of bleeding. For patients describing bleeding events, investigate for an underlying cause (including requesting new bloods)
Adherence	Ideally with inspection of medication in addition to appropriate questioning. Any missed doses. Re-educate on importance of strict intake schedule
Other side effects	Report via yellow card if appropriate
Change in co-medication	Any change to prescription drugs, over the counter drugs or herbal medicines
Re-assessment of risk scores	Re-assess **CHA_2DS_2-VASc score** and **ORBIT-AF bleeding score** at least annually
Re-assessment of optimal DOAC dosing	Confirm patient remains on correct dose based upon the dosing guidance outline above
Blood monitoring	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)

<table>
<tr><td></td><td colspan="5">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</td></tr>
<tr><td rowspan="4">Establish frequency of ongoing reviews</td><td>DOAC</td><td colspan="3">Baseline Renal Function</td><td>FBC</td><td>LFT</td></tr>
<tr><td>Apixaban</td><td>15-29ml/min</td><td>30-59ml/min</td><td>>60ml/min</td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td>Edoxaban
Rivaroxaban</td><td>3 Monthly</td><td>6 Monthly</td><td>12 Monthly</td></tr>
<tr><td>Dabigatran</td><td>Contraindicated</td><td>6 Monthly</td><td>12 Monthly</td><td>12 Monthly</td><td>12 Monthly</td></tr>
</table>

References

NICE. Atrial Fibrillation. Diagnosis and management. NICE Guidelines {NG196}. 27th April 2021.

NICE. Venous Thromboembolic Diseases. Diagnosis, management and thrombophilia testing. NICE Guidelines {NG158}. 26th March 2020.

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STOP A STROKE: AF Oral anticoagulant FAQ. aff8f7_77531df470304bf8a0e47db86ea5f9a5.pdf (filesusr.com)

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PLEASE ENSURE THAT ALL QUESTIONS ARE ANSWERED – IF NOT APPLICABLE PLEASE PUT N/A

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