Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

All Wales Advice on Oral Anticoagulation for Non-valvular Atrial Fibrillation

February 2022

This document has been prepared by a multidisciplinary anticoagulation subgroup, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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1.0 Introduction

1.1 All Wales Medicines Strategy Group guidance

All Wales Medicines Strategy Group (AWMSG) therapeutic guidance is suitable for local adaptation within NHS Wales.

2.0 Background

The guidance document 'Advice on the Role of Oral Anticoagulants for the Prevention of Stroke and Systemic Embolism in People with Atrial Fibrillation' was endorsed by AWMSG in October 2012.

In June 2014, the National Institute for Health and Care Excellence (NICE) Clinical Guideline (CG) 180: *Atrial fibrillation: the management of atrial fibrillation* was published. In response to the publication of this guideline and changes in the evidence, range of therapeutic agents and licensed indications of the newer oral anticoagulants, a multidisciplinary anticoagulation subgroup with membership from across Wales reviewed and updated the recommendations from 2012. The updated document, 'All Wales Advice on the Role of Oral Anticoagulants' was endorsed by AWMSG in September 2014.

In February 2016, this guidance was reviewed and recommendations on the choice of agent were updated to take account of the availability of edoxaban.

In June 2019, the guidance on treatment of patients with non-valvular atrial fibrillation (NVAF) was reviewed and an updated version was published that incorporated the AWMSG-endorsed 'Risk/Benefit Assessment Tool for Oral Anticoagulant Treatment in People with Atrial Fibrillation' (originally published in October 2013), and recommendations from 'Warfarin Monitoring' (originally published in June 2012) relevant to the treatment of NVAF. The updated document, 'All Wales advice on Oral Anticoagulation for Non-valvular Atrial Fibrillation', was endorsed by AWMSG in March 2020.

In June 2021, in response to new evidence regarding assessment of stroke and bleeding risks, NICE Clinical Guideline 180 (CG180) *Atrial fibrillation: Management* was updated and replaced by NICE Guideline 196 (NG196) *Atrial fibrillation: diagnosis and management*[1]. This AWMSG guideline has been updated to incorporate those recommendations; including re-positioning direct oral anticoagulants before vitamin k antagonists (e.g. warfarin) in the treatment pathway.

2.1 Terminology

The term 'direct oral anticoagulants (DOACs)' is used throughout this document to refer to apixaban, dabigatran etexilate, edoxaban and rivaroxaban▼.

Vitamin K antagonists (VKAs) include acenocoumarol, phenindione and warfarin. Warfarin accounts for 99.84% of VKA items prescribed in primary care in Wales. This paper uses the term 'warfarin' to improve readability. However, source guidance using the term VKA has been retained.

2.2 Key sources

Previously developed AWMSG guidance on anticoagulation was used, as well as:

- Scottish Intercollegiate Guidelines Network (SIGN) – Prevention of stroke in patients with atrial fibrillation: a guide for primary care (2014)
- NICE NG196: Atrial Fibrillation: diagnosis and management (2021)
- SIGN 129. Antithrombotics: indications and management (2013)
- European Heart Rhythm Association (EHRA) – Practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation (2018)
- PrescQIPP. East of England Priorities Advisory Committee (PAC) – Atrial fibrillation anticoagulant clinical decision aid (2018)

2.2.1 Key policy documents, reports and national audits

- NHS Wales Delivery Framework and Reporting Guidance 2019-2020

2.2.2 Related national guidance

- NICE NG158: Venous thromboembolic diseases (2020)
- 1000 Lives Plus Improving Medicines Management – Reduction in INR > 5 and INR > 8 in hospital and community settings (2012)

2.3 Existing indicators and measures

2.3.1 NICE Quality Standard 93: Atrial fibrillation and associated measures

Statement 1: Adults with non-valvular atrial fibrillation and a CHA_2DS_2-VAS_C stroke risk score of 2 or above are offered anticoagulation.
Statement 2: Adults with atrial fibrillation are not prescribed aspirin as monotherapy for stroke prevention.
Statement 3: Adults with atrial fibrillation who are prescribed anticoagulation discuss the options with their healthcare professional at least once a year.
Statement 4: Adults with atrial fibrillation taking a vitamin K antagonist who have poor anticoagulation control have their anticoagulation reassessed.
Statement 5: Adults with atrial fibrillation whose treatment fails to control their symptoms are referred for specialised management within 4 weeks.
Statement 6 (developmental): Adults with atrial fibrillation on long-term vitamin K antagonist therapy are supported to self-manage with a coagulometer.

Further resources

- NICE NG203 Chronic kidney disease: assessment and management (2021)
- Greater Manchester Medicines Management Group – Prescriber Support Tool: Direct Oral Anticoagulants (DOACs) for Adults (2020)
- Specialist Pharmacy Service – Direct Acting Oral Anticoagulants (DOACs) in Renal Impairment: Practice Guide to Dosing Issues (2020)

For further information, see the AWMSG website: www.awttc.nhs.wales

3.0 Recommendations

Table 1. Recommendations on the Role of Oral Anticoagulant Treatment in People with non-valvular atrial fibrillation (NVAF)

1.0	Identification
1.1	Non-valvular atrial fibrillation refers to atrial fibrillation in the absence of a mechanical prosthetic heart valve or moderate-to-severe mitral stenosis (usually of rheumatic origin).
1.2	Perform manual pulse palpation to assess for the presence of an irregular pulse that may indicate underlying NVAF in people presenting with any of the following: • breathlessness/dyspnoea • palpitations • syncope/dizziness • chest discomfort • stroke/transient ischaemic attack[1].
1.3	Perform an 12-lead electrocardiogram (ECG) in all people, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected[1].
1.4	In people with suspected paroxysmal atrial fibrillation[1] undetected by 12-lead ECG recording: • use an ambulatory ECG monitor, event recorder or other ECG technology for a period appropriate to detect atrial fibrillation if symptomatic episodes are more than 24 hours[1]. • use a 24-hour ambulatory ECG monitor if asymptomatic episodes are suspected or symptomatic episodes are less than 24 hours apart[1].
2.0	**Initial assessment**
2.1	People with NVAF should have a documented: • stroke and bleeding risk assessment (including pre-treatment blood tests: full blood count [FBC], urea and electrolytes, liver function tests, coagulation screen and international normalised ratio [INR]); • discussion with the clinician about the risks and benefits of treatment (consider NICE recommendations on shared decision making).
2.2	When a person is initiated on oral anticoagulants in one care setting, the documented baseline assessment should be transferred with the prescribing responsibility.
2.3	The focus of NVAF management should be to identify affected people and undertake a stroke risk assessment using the CHA_2DS_2-VASc risk assessment tool. Bleeding risk should also be assessed using an appropriate tool, such as the ORBIT bleeding risk score[2], and modifiable risk factors should be addressed. See section: AWMSG Risk/Benefit Assessment Tool for Oral Anticoagulant Treatment in People with NVAF. This tool supports a consistent approach

	for people with AF and incorporates the CHA_2DS_2-VASc risk assessment tool and the ORBIT* bleeding risk score. Discuss the results of the assessments of stroke and bleeding risk with the person. Offer monitoring and support to modify risk factors for bleeding such as uncontrolled hypertension, concurrent medication (e.g. antiplatelets), harmful alcohol consumption and reversible causes of anaemia[1].
2.4	Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account[1]. Consider anticoagulation for men with a CHA_2DS_2-VASc score of 1. Take the bleeding risk into account[1].
3.0	**Choice of agent**
3.1	Do not offer aspirin monotherapy solely for stroke prevention to people with NVAF[1].
3.2	Anticoagulation may be with a direct acting oral anticoagulant (DOAC) (apixaban, dabigatran etexilate, edoxaban or rivaroxaban▼) or warfarin. Discuss the treatment options for anticoagulation with the person and base the choice on their clinical features and preferences[1]. See Appendix 1 to compare information on warfarin and available DOACs. Discuss the fact that for most people the benefit of anticoagulation outweighs the bleeding risk, but for people with an increased risk of bleeding that balance may differ or may require additional monitoring[1]. Consider using a patient decision aid (such as the Anticoagulation Decision Support Tool†). This helps people reach a decision about whether to take an oral anticoagulant to reduce the risk of stroke. If no anticoagulation preference exists, anticoagulation should be initiated with a DOAC[1]. Take into account any contraindications for each DOAC and follow the guidance in the British National Formulary, Summary of Product Characteristics and the MHRA advice on DOACs, in particular for advice on dosages in people with renal impairment, reversal agents and monitoring (See Appendix 1)[1]. Warfarin can be used as an alternative if DOACs are contraindicated, not tolerated or not suitable. DOACs should not be used in patients with a mechanical heart valve associated with AF – see MHRA advice on inappropriate anticoagulation of patients with a mechanical heart valve[3].

* Evidence has shown that the ORBIT bleeding risk tool has a higher accuracy in predicting absolute bleeding risk than other bleeding risk tools[1].

† At the time of writing (September 2021) the Anticoagulation Decision Support Tool does not reflect the latest NICE guidance (NG196). However, updates to the tool are under consideration.

3.3	The decision about whether to start treatment with warfarin or a DOAC should be made after an informed discussion between the clinician and the patient about the risks and benefits[4-7]. In selecting the specific anticoagulant to use for the prevention of stroke and systemic embolism in people with NVAF, consider: • **Initiation of warfarin and DOACs**: – Warfarin may be initiated in primary care for NVAF using a slow-loading regime. A slow-loading regimen is appropriate for patients who do not require rapid anticoagulation for NVAF. This is safe and achieves therapeutic anticoagulation within 3-4 weeks for the majority of patients. There are several evidence-based protocols; e.g. prescribe 3 mg warfarin daily for five days, then check International Normalised Ratio (INR) on the fifth day. Please refer to Directed Enhanced Service: Oral Anticoagulation with Warfarin for further information[8]. • For DOACs, please refer to Appendix 1 and manufacturer's full prescribing information for standard doses and dosage reductions to account for renal impairment, age and body weight**. Monitoring of effects of warfarin and DOACs**: – Warfarin has a narrow therapeutic index and a long half-life (40 hours)[9], as well as significant interpatient variability; therefore regular INR blood monitoring tests are required to guide dosing. The British Society for Haematology (BSH) recommend a target INR of 2.5 for atrial fibrillation[10]. – INR testing should be frequent for the first few weeks or months then normally every 1–2 months in NVAF. This provides an opportunity to monitor adherence, effectiveness and safety. – Self-monitoring of warfarin is an option once the patient is receiving a stable dose. – Level of anticoagulation is never monitored with a DOAC – if monitoring does occur, this is for drug levels only‡. – See the MHRA advice on Warfarin and other anticoagulants – monitoring of patients during the COVID-19 pandemic. • **Access to a licensed product for rapid reversal of the anticoagulant effect**: – Idarucizumab (Praxbind ®) is the licensed antidote for dabigatran etexilate[11] (refer to local guidelines on how and when to use this). Andexanet alfa (Ondexxya▼®) is a licensed antidote for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding[12,13]. Both antidotes are suitable for hospital prescribing only and Andexanet alfa should be used in line with NICE technology appraisal recommendations (TA697[13]).

‡ With certain reagents, prolongation of the prothrombin time (PT)/activated partial thromboplastin time (APTT) can be seen but this cannot be used to calibrate activity. For dabigatran etexilate, the thrombin clotting time (TCT) is also a useful test. Apixaban, edoxaban and rivaroxaban▼ levels can be measured with a calibrated quantitative anti-factor Xa assay.

  - There is no specific licensed antidote for edoxaban; clinical trials are ongoing[14]. The summary of product characteristics (SPC) states the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of edoxaban 30 minutes after completing the infusion[15].
  - The anticoagulant effect of warfarin can be reversed using phytomenadione (vitamin K_1)[9,16] – refer to the All Wales Warfarin Chart for advice on how this should be performed.
- **Experience**: Warfarin has been used for more than 60 years, its short and long-term side effect profiles are well-described.
- **Renal function in NVAF**:
  Edoxaban is associated with decreasing efficacy with increasing creatinine clearance. The SPC advises edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk[15].
- **Renal impairment**:
  - Dose reduction (or sometimes avoidance) of DOACs is required in people with renal impairment (see Appendix 1)[15,17-19]. Risk of bleeding may increase as renal function declines[20].
  - Renal impairment is not a contraindication for warfarin use, although an increased frequency of INR monitoring is recommended.
  - See NICE NG203[21] and Specialist Pharmacy Service guidance on DOACs in renal impairment for more information on anticoagulation in chronic kidney disease.
- **Extremes of BMI**:
  - The relative dose of DOACs may vary by 20–30% at extremes of bodyweight (< 50–60 kg or > 100–120 kg). This may be problematic given the difficulties in monitoring the therapeutic effects[22]. The SPC for rivaroxaban▼, states no dose adjustment is necessary in extremes of body weight[19].
  - Guidelines from the International Society on Thrombosis and Haemostasis (ISTH) recommend not using a DOAC in people > 120 kg or with a BMI > 40 due to limited clinical data available for this patient group[23].
    - However, the ISTH guidelines recommend that if a DOAC is to be commenced in a person who is > 120 kg or has a BMI > 40 then drug-specific peak and trough level should be measured. If the level falls within the expected range, consensus opinion from the international guidelines is to continue the DOAC[23].
    - In 2021, the ISTH guidelines recommend not to regularly follow peak or trough drug-specific DOAC levels. However, the updated recommendations relate to DOAC use for the treatment and prevention of venous thromboembolism[24].
    - Please refer to local health board guidance.
  - See warfarin SPC.
  - Anticoagulation (warfarin or DOAC) in patients < 50 kg should be used with caution.

- **Risk of haemorrhage**: Where a centre (e.g. individual hospital) has INR Time of Therapeutic Range (TTR) of ≤ 65%, DOACs have been demonstrated to have a lower risk of major intracerebral haemorrhage than warfarin. This difference may be reduced if the centre's TTR is over 65%[25]. DOACs are generally associated with a slightly higher risk of gastrointestinal haemorrhage[25], although apixaban has demonstrated a comparable rate of gastrointestinal bleeding versus warfarin[18].
- **Interactions**:
  - Warfarin has many listed interactions. Careful INR monitoring can often pre-empt over- or under-coagulation. Advise people to minimise major changes in paracetamol use and not to use any over the counter medications or dietary supplements without checking with the healthcare team first[26].
  - DOACs have a number of listed interactions for which the advice is to avoid concomitant use (see eBNF[27] and SPCs). Patients co-administered medication that may inhibit metabolism and potentiate bleeding risk with DOACs are managed more safely on warfarin, as the INR may be adjusted accordingly[22].
- **Time in therapeutic range**: DOACs are likely to be more beneficial in patients whose INR on warfarin is regularly outside the therapeutic range despite good medication adherence[22].
  - See AWMSG Recommendations 3.4 and 4.4.
- **Adherence**:
  - See AWMSG Recommendation 3.4.
  - Warfarin is long-acting and is taken once daily.
  - It is important to take a DOAC as recommended. For NVAF, this is once a day (edoxaban or rivaroxaban▼) or twice a day (apixaban or dabigatran etexilate) (see Appendix 1). The protective effect of the DOAC on the risk of stroke may fade 12–24 hours after a dose[28].
- **Monitored dosage systems**: Dabigatran etexilate is not suitable for use in a monitored dosage system[22§].
- **Switching from warfarin**: The potential benefits of DOACs should be considered against their potential risks, taking into account the person's level of INR control.
  - According to the individual SPCs, warfarin should be discontinued and DOAC should be started when INR ≤ 2 (apixaban, dabigatran etexilate)[17,18], INR ≤ 2.5 (Edoxaban)[15], INR ≤ 3 (rivaroxaban▼)[19]. All prescribing choices should be made according to the relevant SPC.
- **Diet**:
  - Rivaroxaban▼ should be taken with food.
  - Warfarin – Advise people that consumption of alcohol should be limited to only within the recommended limits[26].
  - Warfarin – Certain foods such as liver, broccoli, Brussels sprouts and green leafy vegetables contain large amounts of vitamin K.

§ Not suitable for standard monitored dosage systems; a specific dabigatran etexilate adherence aid can be provided.

	Sudden changes in diet, including cranberry juice, grapefruit juice, can potentially affect control of anticoagulation. • **Cancer patients requiring anticoagulation:** If patients develop cancer, their risk of thromboembolism and bleeding will change. Given the heterogonous nature of patients with cancer, their risks and benefits for continued anticoagulation should be assessed individually and reviewed periodically[29]. The International Society on Thrombosis and Haemostasis has developed guidance on the anticoagulation of patients with cancer and non-valvular atrial fibrillation receiving chemotherapy[30]. • **Risk of recurrent thrombotic events in patients with antiphospholipid syndrome:** MHRA advises DOACs are not recommended in patients with antiphospholipid syndrome, particularly high-risk patients (those who test positive for all 3 antiphospholipid tests — lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies). Consider a vitamin K antagonist such as warfarin[31]. Those initiating warfarin or DOACs should have access to local resources on the use of these medicines e.g.: • See section: AWMSG Risk/Benefit Assessment Tool for Oral Anticoagulant Treatment in People with NVAF • **Atrial Fibrillation Decision Support Tool** (www.anticoagulation-dst.co.uk/)**. • UKMi Common Questions and Answers on the Practical Use of Oral Anticoagulants in Non-Valvular Atrial Fibrillation. Additional resources that may be of interest: CKS Summary: Anticoagulation – oral.
3.4	The prescriber should make efforts to understand and address the reasons for non-adherence before switching to an alternative medicine. Poor adherence to any oral anticoagulant regimen is likely to be associated with increased risk of thrombosis or bleeding.
3.5	If poor anticoagulation control (see AWMSG Recommendation 4.4) cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person[28].
3.6	Ensure that people prescribed anticoagulants receive appropriate verbal and written information when necessary throughout the course of their treatment[15] and are advised to carry an alert card with them at all times[32,33]. People initiated on warfarin should be issued the information (yellow) booklet. People initiated on a DOAC should be provided with written information, an alert card, and a monitoring booklet, e.g. the European Heart Rhythm Association (EHRA) Atrial Fibrillation Oral Anticoagulation Card[34].

** At the time of writing (September 2021) the Atrial Fibrillation Decision Support Tool does not reflect the latest NICE guidance (NG196). However, updates to the tool are under consideration.

3.7	In people with NVAF (and in the absence of other clinical conditions such as recent acute coronary syndrome) the combination of aspirin and warfarin is not recommended[26]. If warfarin is indicated for moderate- or high-risk NVAF it should be used alone, even in the presence of concomitant stable cardiovascular disease[26].
3.8	Combination therapy of warfarin and antiplatelet may be advised by cardiologists, normally for a limited period, for people who have had coronary artery stents or cardiology intervention in the previous year. Clarification should be sought from the patient's interventional cardiologist if there is any doubt[35].
4.0	**Review**
4.1	Where warfarin is prescribed, there should be a documented process to systematically assess the TTR for each person. See also NICE QS93 Statement 4 for suggested measures. Discuss the option of switching treatment to a DOAC at next routine appointment, taking into account the TTR for the patient[1]. Where DOACs are prescribed, there should be a documented process to systematically assess treatment (see Specialist Pharmacy Service Monitoring DOACs).
4.2	For people who are taking an anticoagulant, review the need for anticoagulation and the quality of anticoagulation at least annually, or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk[1] (see section: AWMSG Risk/Benefit Assessment Tool for Oral Anticoagulant Treatment in People with NVAF).
4.3	Undertake Full Blood Count (FBC), renal and liver function tests at least annually for people taking any anticoagulant[36]. **More frequent monitoring is advised if baseline tests are abnormal or there is intercurrent illness that may impact renal or hepatic function**. The European Heart Rhythm Association suggests that if the Creatinine Clearance (CrCl) is ≤ 60 ml/minute, the frequency of monitoring (in months) can be guided by the CrCl divided by 10. For example, if the creatinine clearance is 30 ml/minute then the renal function (and the prescribed dose) should be reassessed every 3 months[37].
4.4	Reassess anticoagulation (see Recommendation 4.5) for a person with poor anticoagulation control shown by a TTR of less than 65%[1] over 6 months (see AWMSG Recommendation 6.0). Consider also using the following as indicators of poor anticoagulation control: • 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.
4.5	When reassessing anticoagulation, take into account and if possible—address the following factors that may contribute to poor anticoagulation control, using national or locally agreed tools: • cognitive function

	• adherence to prescribed therapy • new diagnoses e.g. cancer • interacting drug therapy e.g. over the counter therapies, frequent antibiotics • lifestyle factors including diet and alcohol consumption. Do not withhold anticoagulation solely because the person is at risk of having a fall[1].
4.6	For people with AF who are not taking an anticoagulant, review stroke risk when they reach age 65 or if they develop any of the following at any age: • diabetes • heart failure • hypertension • peripheral arterial disease • coronary heart disease • stroke, transient ischaemic attack or systemic thromboembolism[1].
4.7	For people with AF who are not taking an anticoagulant because of bleeding risk or other factors, review stroke and bleeding risks annually, and ensure that all reviews and decisions are documented[1].
5.0	**Prescribing responsibility**
5.1	People with a new diagnosis of non-valvular AF should normally have the initial assessment and discussion regarding anticoagulation in the setting (hospital, GP practice) in which the diagnosis was made.
5.2	When a decision to initiate anticoagulation has been made, prompt initiation and stabilisation* should normally be undertaken in the setting in which the decision was made. If a primary care team does not have appropriate expertise to initiate warfarin or a DOAC a baseline assessment should be sent to the oral anticoagulant clinic. The clinic will provide patient education and counselling but will not advise on the decision to initiate treatment. **Stabilisation: Two INR readings in range with confirmation that INR/dosing interval at least 7 days.*
5.3	When a person is identified as having poor anticoagulation control, the re-assessment of anticoagulation should be undertaken through discussion with the patient, by the healthcare professional providing dosing. Anticoagulant clinics may need to liaise with the GP practice following a re-assessment of poor anticoagulant control to identify further possible causes. If poor anticoagulation control cannot be improved as a result of this reassessment, the risks and benefits of alternative stroke prevention strategies should be evaluated and discussed with the person.
5.4	In the hospital setting, the decision to start therapy with a DOAC for non-valvular AF should be carried out by clinicians whose scope of practice includes stroke prevention and management of AF.

	It may be appropriate for GP practices, particularly those that provide warfarin dosing services, to make the decision to start a DOAC depending on health board service models.
5.5	The cause of a raised INR (INR > 8 or repeated INR of 6 or 7) should be investigated. This should normally be undertaken by the team requesting the INR.
6.0	**Monitoring of INR control (Warfarin only)**
6.1	When calculating TTR: • Use a validated method of measurement such as the Rosendaal method for computer-assisted dosing[38], or proportion of tests in range for manual dosing. • Exclude measurements taken during the first 6 weeks of treatment. • Calculate TTR over a maintenance period of at least 6 months[1].
6.2	Warfarin dosing: • Providers should normally use computer dosing software systems. The National Patient Safety Agency (NPSA) states: '*There is evidence that anticoagulant dosing software helps to maintain the INR levels within the therapeutic range, extend the time between INR tests and effectively manage anticoagulant records facilitating service audit*'[32]. The management of non-attenders, recall facility, annual review and audit features, as well as serious incident review, are all important in ensuring delivery of a safe system to patients. • Computer dosing should be interpreted and actioned by non--administrative professionals, who are trained, accredited and competent to manage warfarin therapy. • Avoid over-reliance on computer-generated dosing and use clinical expertise to interpret dosing advice.
6.3	Self-monitoring of coagulation status in adults and children on long-term VKA therapy should be in accordance with NICE DG14 Atrial fibrillation and heart valve disease: self-monitoring coagulation status using point-of-care coagulometers if: '*the person prefers this form of testing, **and** the person or their carer is both physically and cognitively able to self-monitor effectively'*[39]*.*
7.0	**Management of supra therapeutic INR's (Warfarain only)**
7.1	People with mechanical valves with INR over 8 should be managed according to specialist advice. Please refer to health board specific guidelines.
7.2	It is appropriate to administer oral phytomenadione (vitamin K1) in general practice as well as in the hospital setting for people with INR > 8, with no bleeding where the perceived risk of bleeding is high. **Exceptions:** AWMSG Recommendation 7.1.
7.3	Give phytomenadione (vitamin K1) 1–5 mg by mouth using the intravenous preparation orally (unlicensed use); repeat dose of phytomenadione if INR still too high after 24 hours; restart warfarin when INR < 5[27]. Expert opinion suggests that 2 mg is an adequate dose. Access to vitamin K – Practices, community pharmacists and out of hours providers may wish to stock phytomenadione or agree local arrangements to ensure prompt access to therapy.

8.0	**Use of low molecular weight heparin (LMWH) for subtherapeutic INR (Warfarin only)**
8.1	Selected patients on warfarin who are at high risk of thromboembolism (for example, patients with mechanical valves or recurrent deep vein thrombosis/pulmonary embolism (DVT/PE) and those identified by the haematologist or cardiac surgeon) should be co-prescribed LMWH if the INR becomes subtherapeutic (unlicensed indication). LMWH prescribing in these circumstances should be undertaken by the department responsible for dosing warfarin[29].
9.0	**Reporting**
9.1	Due to newer licensed indication(s), rivaroxaban▼ is currently under 'Additional Monitoring' by the European Medicines Agency (EMA) and all suspected adverse drug reactions (ADRs) should be reported, as well as all serious ADRs (see yellowcard.mhra.gov.uk for definition of serious) to apixaban, dabigatran etexilate, edoxaban and warfarin. ADRs should be reported directly to the Medicines and Healthcare Products Regulatory Agency (MHRA) through the Yellow Card Scheme using the electronic form at yellowcard.mhra.gov.uk or cards available at the back of the British National Formulary (BNF).

4.0 All Wales risk/benefit assessment tool for oral anticoagulation treatment in people with NVAF

This tool presented overleaf supports a consistent approach for people with NVAF, both in hospital and GP settings, to promote:

- an assessment of stroke risk,
- an assessment of bleeding risk,
- effective annual assessment, and
- data collection/audit trail.

Assessment tool is provided on pages 15–20

All Wales risk/benefit assessment tool for oral anticoagulant treatment in people with non-valvular atrial fibrillation

To be completed and documented prior to initiating treatment with oral anticoagulant and as an annual review for patients taking oral anticoagulants.

Patient addressograph	**Weight (kg):** **Cr (µmol/l):** **CrCl (ml/min):***	**Consultant:** **Ward/Clinic:** **GP Details:** **Date:**
* To calculate CrCl, use of a web-based application such as MDCalc which uses actual bodyweight, is suggested. If the patient's height is also provided the different weight calculation methods (modified for body weight) can be seen giving a range of possible values for CrCl. Where these results cross (or are close to) a CrCl level that may require a dose change, this can support the clinician making a dosing decision[20].		

The focus of NVAF management should be to identify affected people and undertake a stroke risk assessment using the CHA_2DS_2-VASc risk assessment tool, for people with any of the following:

- symptomatic or asymptomatic paroxysmal, persistent or permanent AF
- atrial flutter
- a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm.

Please ensure all patients starting anticoagulants have baseline full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFTs), coagulation screen and international normalised ratio (INR).

CHA_2DS_2-VASc scoring system (stroke risk stratification scheme)

Risk factor		Points	Score
None		0	
C	Heart failure/left ventricular dysfunction	1	
H	Hypertension	1	
A_2	Age ≥ 75	2	
D	Diabetes mellitus	1	
S_2	Stroke/transient ischaemic attack (TIA)/thromboembolism	2	
V	Vascular disease	1	
A	Age 65–74	1	
Sc	Female	1	
		Total	

Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, unless contraindicated, taking bleeding risk into account.

Consider anticoagulation for men with a CHA_2DS_2-VASc score of 1, unless contraindicated, taking the bleeding risk into account.

Contraindications†† (see product SPC or BNF for full details)	**Please tick all that apply**
A lesion or condition, if considered a significant risk factor for major bleeding. This may include:	
current or recent gastrointestinal ulceration	
significant thrombocytopenia (platelet count < 50 x 109/L) – refer to haematologist	
presence of malignant neoplasm at high risk of bleeding	
within 72 hours of major surgery with risk of severe bleeding – defer and reassess risk postoperatively	
recent brain or spinal injury	
recent brain, spinal, or ophthalmic surgery	
acute clinically-significant bleed – defer and re-assess stroke versus bleeding risk within 3 months	
decompensated liver disease or deranged baseline clotting screen (INR > 1.5)	
hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C	
known large oesophageal varices	
during pregnancy or within 48 hours post-partum – seek urgent haematological advice	
arteriovenous malformation	
vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities	
sustained uncontrolled hypertension: systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg	
Concomitant treatment with any other anticoagulant agent	
Previously documented hypersensitivity to either the drug or excipients	

Assess bleeding risk using an appropriate tool, such as ORBIT, and address modifiable risk factors.

††There are licensed antidotes for dabigatran etexilate, apixaban and rivaroxaban▼ (suitable for hospital prescribing only). There is no specific licensed antidote for edoxaban, clinical trials are ongoing. The anticoagulant effect of warfarin can be reversed using phytomenadione (vitamin K1). Please consult the product information for advice on treatment in the event of bleeding complications, or overdose. A full list of contraindications, warnings and information on posology can be found in the individual Summaries of Product Characteristics for apixaban, dabigatran etexilate, edoxaban, rivaroxaban▼ and warfarin.

ORBIT scoring system (risk assessment for bleeding in AF patients who are starting or have started anticoagulation)

ORBIT bleeding score: Clinical characteristics	Points	Score
Reduced haemoglobin (< 13 g/dL for males and < 12 g/dL for females), haematocrit (< 40% for males and < 36% for females)	No = 0 Yes =2	
Age > 74 years	No = 0 Yes = 1	
Bleeding history Any history of GI bleeding, intracranial bleeding, or haemorrhagic stroke	No = 0 Yes = 2	
GFR < 60 mL/min/1.73 m2	No = 0 Yes = 1	
Treatment with antiplatelet agents	No = 0 Yes = 1	
	Total	

Interpretation of ORBIT bleeding score

Orbit score	Risk group	Bleeds per 100 patient years
0 – 2	Low risk	2.4
3	Medium risk	4.7
4 – 7	High Risk	8.1

The ORBIT score should not be used to exclude patients from oral anticoagulant therapy, but allows clinicians to make an informed assessment of bleeding risk and, importantly, ensures correctable risk factors for bleeding (e.g. concomitant use of antiplatelets) are considered.

Other clinical/social factors to be considered‡‡

Other clinical and social factors for consideration	Yes	No	Action/ Date
Is the patient being investigated for or receiving treatment for cancer? AF + cancer: given the heterogeneous nature of patients with cancer, the risks and benefits for continued anticoagulation should be assessed individually and reviewed periodically[40].			
Is the patient taking any other medication, including over the counter medication; vitamins; minerals; herbal supplements? Refer to Summaries of Product Characteristics for advice on use of DOACs and warfarin with other medicines.			
Is there evidence of trips or falls?			
Does the patient have any sensory, visual or literacy deficits without carer support?			
Does the patient use/require the use of a multi-compartment compliance aid (MCA)?			
Is there any evidence of dementia or possible problems with mental capacity?			
Is the patient of child bearing age?			
At annual review, also check:			
Adherence (check time in therapeutic INR range if on warfarin)			
Has the patient had any thrombotic events?			
Has the patient experienced any bleeding events?			
Has the patient experienced any other side effects?			
Has the patient experienced any hospital admission related to the anticoagulant?			
Check renal function: impaired renal function may constitute a contraindication or recommendation not to use the anticoagulant medicine, or may require a dose reduction; recommendations differ for warfarin, apixaban, dabigatran etexilate, edoxaban and rivaroxaban▼.			

Initial assessment	
CHA_2DS_2-VASc score	
Contraindications?	
ORBIT score N.B. In patients with an ORBIT score ≥ 3, caution and regular review are appropriate.	
Other clinical/social factors checked?	
Has the patient had baseline U&Es, LFTs, FBC and coagulation screen?	

‡‡ Adapted from risk/benefit tool produced by Haematology Department, Royal Gwent Hospital.

Choice of agent and dose

Refer to Appendix 1 and manufacturer's full prescribing information for advice on dosage reductions for renal impairment, age and body weight.

Agent *Licensed indication*	**Please tick**	**Rationale for decision and dose prescribed**
No anticoagulant or thromboprophylaxis given		
Apixaban *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors:* • *Previous stroke or transient ischemic attack* • *Age 75 years and above* • *Diabetes mellitus* • *symptomatic heart failure (NYHA ≥2)* • *hypertension.*		
Dabigatran etexilate *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors:* • *Previous stroke or transient ischemic attack* • *Age 75 years and above* • *Diabetes mellitus* • *symptomatic heart failure (NYHA ≥2)* • *hypertension.*		
Edoxaban *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors:* • *Previous stroke or transient ischemic attack* • *Age 75 years and above* • *Diabetes mellitus* • *congestive heart failure* • *hypertension.*		
Rivaroxaban▼ *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors:* • *Previous stroke or transient ischemic attack* • *Age 75 years and above* • *Diabetes mellitus* • *congestive heart failure* • *hypertension.*		
Warfarin *For prophylaxis of systemic embolism in patients with rheumatic heart disease and AF*		
Other (Please state)		

Patient discussion	Please tick
Patient/carer understands the purpose for anticoagulation, intended duration of treatment and agrees with decision to prescribe antithrombotic medication.	
Patient/carer understands risks and benefits of anticoagulant medication.	
Patient/carer understands dosing regimen, importance of adherence, timing of doses and what to do if doses are missed.	
Patient/carer is aware to seek pharmacist advice before buying herbal or over the counter (e.g. NSAIDs) as they may interact with the antithrombotic medication.	
Patient/carer is aware of the signs and symptoms of unusual bleeding and what to do if bleeding or injury occurs.	
Written information provided i.e. anticoagulation booklet and to carry alert card at ALL times.	

Follow up date and who with:	
Prescriber name (print)	
Signature	
Bleep No/Ext	
Authorising consultant	
Date	

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Appendix 1: Anticoagulant comparison table

	Warfarin (view SPC)	Apixaban (view SPC)	Dabigatran etexilate (view SPC)	Edoxaban (view SPC)	Rivaroxaban▼ (view SPC)
Licensed indications	Prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation	Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more of the following risk factors: • Previous stroke or transient ischemic attack • Age 75 years and above • Diabetes mellitus • symptomatic heart failure (NYHA ≥2) or congestive heart failure* • Hypertension.			
Doses	According to INR (Target INR 2.5)	5mg twice daily	150 mg twice daily (Age < 80 yrs) 110 mg twice daily in: • Age ≥ 80 years • Concomitant treatment with verapamil	60 mg once daily	20 mg once daily
Mechanism of action	Vitamin K antagonist	Direct inhibitor of factor Xa	Direct thrombin inhibitor	Direct inhibitor of factor Xa	Direct inhibitor of factor Xa
Dose reduction	Monitor INR more frequently in patients at an increased risk of over coagulation e.g. patients with severe hypertension, liver or renal disease	2.5 mg twice daily in patients with CrCl 15-29 mL/min or 2 or more of the following: • age ≥ 80 years • body weight ≤ 60 kg • serum creatinine ≥ 133 umol/l	Consider dose reduction if: • Increased risk of bleeding • age 75-80 years • patients with gastroesophageal reflux, oesophagitis or gastritis • CrCL 30-50 mL/min	30 mg once daily in patients with one or more of the following clinical factors: • CrCl 15-50 ml/min • Body weight ≤ 60 kg • Concomitant P-glycoprotein inhibitors – ciclosporin, dronedarone, erythromycin, or ketoconazole	15 mg once daily in patients with: • CrCl 30-49 ml/min • CrCl 15-29 mL/min (use with caution)
Drug interactions†	Warfarin has a narrow therapeutic range and care is required with all concomitant therapy	Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole and posaconazole. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort.	Avoid with HIV protease inhibitors, rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort, dronedarone, ciclosporin, tacrolimus, ketoconazole, itraconazole. Caution with amiodarone, and verapamil.	No data on co-administration with HIV protease inhibitors. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort.	Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole, posaconazole and dronedarone. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort.
Contraindication due to renal impairment†		CrCl < 15 ml/min	CrCl < 30 ml/min	CrCl < 15 ml/min	CrCl < 15 ml/min
Efficacy for stroke prevention	Warfarin has been used for over 60 years and has proven long term efficacy	Superior to warfarin (ARISTOTLE trial)[6,18]. *Note: Approximately 5% of the study population received 2.5 mg apixaban*[41]	Superior to warfarin with 150 mg twice daily dose. Non-inferior to warfarin with 110 mg twice daily dose (RE-LY trial)[5,17]	Non-inferior to warfarin (ENGAGE-AF TIMI 48 trial)[7,15] *Note: Approximately 25 % of population received 30 mg edoxaban*[41]	Non-inferior to warfarin (ROCKET-AF trial)[4,19] *Note: Approximately 21 % of the population received 15 mg rivaroxaban▼*[41]
Administration	Take with / without food Tablets can be crushed and put through nasogastric tube (NOT within licensed indication)	Take with / without food Maybe crushed and put through nasogastric tube if required (within licensed indication)	Swallow whole with or without food Capsules CANNOT be opened as it results in a substantial increase in drug bioavailability	Take with or without food Can be crushed and put through nasogastric tube (NOT within licensed indication)	Take with food. May be crushed and put through nasogastric tube if required (within licensed indication)
Monitored dosage system	Should be kept separate from other medication in compliance aids as the frequently changing doses could cause confusion.	Can be used in compliance aids	Not suitable for compliance aids.	Can be used in compliance aids	Can be used in compliance aids
Reversibility	phytomenadione (vitamin K_1)[9,16] – refer to the All Wales Warfarin Chart for advice	andexanet alfa (Ondexxya®) ▼§[12]	idarucizumab (Praxbind®)	No licensed medicine, clinical trials ongoing. Refer to edoxaban SPC section 4.9, for management of bleeding (with 4 factor PCC)	andexanet alfa (Ondexxya®) ▼§[12]

▼ Newly marketed drugs and vaccines are intensively monitored for a minimum of two years, in order to confirm the risk/benefit profile of the product. Healthcare professionals are encouraged to report all suspected adverse drug reactions.
* 'Symptomatic heart failure' is specific to the licensed indication of apixaban and dabigatran etexilate, 'Congestive heart failure' is specific to the licensed indication of edoxaban and rivaroxaban▼.
† List not exhaustive. Refer to product SPC for full list of drug interactions and contraindications.
§ Should be used in line with NICE technology appraisal recommendation (TA697).
NYHA = New York Heart Association functional classification.

Appendix 2: Patient specific characteristics to consider when choosing a direct oral anticoagulant in non-valvular atrial fibrillation

There are no clinical trials directly comparing DOACs and the following guidance is based on indirect comparisons. The choice of agent and dose should always be specific to each individual patient based on their medical history and circumstances. The guidance below can be considered in consultation with the patient/guardian/carer, and should be informed by the summaries of product characteristics (SPCs) for the relevant drugs, to determine which drug options may be most appropriate for individual patients presenting with the characteristics listed. For full prescribing information consult SPC.

Specific patient characteristics		
No specific patient characteristics or preferences	⇨	Any DOAC can be considered as an option. Consider agent with lowest acquisition cost.
History of GI bleed or high risk	⇨	Consider agent with lowest reported GI bleeding outcomes or adverse effects. *In the clinical trials (RE-LY, Engage & Rocket) higher rates of GI bleeding were reported with dabigatran etexilate 150 mg, rivaroxaban▼ and edoxaban, compared to warfarin[45]. Apixaban was associated with similar risks to warfarin in clinical trials (ARISTOTLE)[43].*
High risk of ischaemic stroke, low bleeding risk and age < 80 years old	⇨	Consider agent with the best reduction of ischaemic stroke. *Dabigatran etexilate 150 mg is the only antithrombotic agent shown to have superior efficacy in the reduction of ischaemic stroke when compared to warfarin (RE-LY trial)[42]*
Previous stroke (secondary prevention)	⇨	Consider agent associated with greatest reduction of secondary stroke. *Subgroup analyses showed favourable efficacy in patients with previous stroke for all DOACs when compared with warfarin[42-44].*
Moderate renal impairment (CrCl 30–50 ml/min)	⇨	Consider agents which are less dependent on the kidney for excretion. *Renal clearance for each DOAC (expressed as a percentage of clearance of total absorbed dose) is[37]:* *Apixaban (27%), rivaroxaban▼ (35%), edoxaban (50%), dabigatran etexilate (80%).*
CAD, previous MI or high risk for ACS/MI	⇨	Consider agent with a positive effect in ACS. *Rivaroxaban▼ is the only licensed DOAC indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS)[44]. Please refer to posology section of rivaroxaban▼ SPC.*
Patient preference	⇨	Consider once-daily formulations.

ACS= acute coronary syndrome; CAD=coronary artery disease; MI = myocardial infarction; GI=gastrointestinal; ▼= drug is subject to additional monitoring