



ALL WALES ADVICE ON THE ROLE OF ORAL ANTICOAGULANTS RECOMMENDATIONS ONLY

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. The updated document was endorsed by AWMSG in September 2014.

It was agreed that the recommendations on choice of agent would be reviewed in one year, and therefore consultation was undertaken and the document updated accordingly.

The full updated document is available at:

www.awmsg.org/docs/awmsg/medman/All%20Wales%20Advice%20on%20the%20Role%20of%20Oral%20Anticoagulants.pdf

2.1 Terminology

The term 'non-vitamin K antagonist oral anticoagulants (NOACs)' 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.

3.0 RECOMMENDATIONS

Table 1. Recommendations on the Role of Oral Anticoagulants for the Prevention of Stroke and Systemic Embolism in People with Non-valvular AF

1.0	IDENTIFICATION
1.1	<p>Perform manual pulse palpation to assess for the presence of an irregular pulse that may indicate underlying AF in people presenting with any of the following:</p> <ul style="list-style-type: none"> • breathlessness/dyspnoea • palpitations • syncope/dizziness • chest discomfort • stroke/transient ischaemic attack (NICE 2014)¹.
1.2	<p>Perform an electrocardiogram (ECG) in all people, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected (NICE 2014)¹.</p>
2.0	INITIAL ASSESSMENT
2.1	<p>People with AF should have a documented:</p> <ul style="list-style-type: none"> • 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, using accredited decision aids where possible (e.g. NICE Patient Decision Aid) (AWMSG 2014).
2.2	<p>When a person is initiated on oral anticoagulants in one care setting, the documented baseline assessment should be transferred with the prescribing responsibility.</p>
2.3	<p>The focus of AF management should be to identify affected people and undertake a stroke risk assessment using the CHA₂DS₂-VASc risk assessment tool. Assess bleeding risk using an appropriate tool, such as HAS-BLED or the AWMSG Risk/Benefit Assessment Tool for Oral Anticoagulant Treatment in People with AF, and address modifiable risk factors.</p>
2.4	<p>Offer anticoagulation to people with a CHA₂DS₂-VASc score of 2 or above, taking bleeding risk into account (NICE 2014 Key Priority for Implementation [KPI])¹.</p> <p>Consider anticoagulation for men with a CHA₂DS₂-VASc score of 1. Take the bleeding risk into account (NICE 2014)¹.</p>
3.0	CHOICE OF AGENT
3.1	<p>Do not offer aspirin monotherapy solely for stroke prevention to people with AF (NICE 2014 KPI)¹.</p>
3.2	<p>Anticoagulation may be with warfarin or a non-vitamin K antagonist oral anticoagulant (NOAC) (apixaban, dabigatran etexilate, edoxaban[▼] or rivaroxaban[▼])... Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences (based on NICE CG180 [2014])¹.</p> <p>Consider using a patient decision aid e.g. NICE Patient Decision Aid. This helps people reach a decision about whether to take an oral anticoagulant to reduce the risk of stroke, and whether to take warfarin or a NOAC.</p> <p>If, after using decision aids (such as NICE Patient Decision Aid and www.anticoagulation-dst.co.uk/), no preference exists, warfarin therapy (time in therapeutic range [TTR] over 65%) is a reasonable therapeutic option (AWMSG 2016).</p>
3.3	<p>The decision about whether to start treatment with warfarin or a NOAC should be made after an informed discussion between the clinician and the person about the risks and benefits²⁻⁵.</p> <p>In selecting the specific anticoagulant to use for the prevention of stroke and systemic embolism in people with non-valvular AF, consider:</p> <ul style="list-style-type: none"> • Monitoring of effects of warfarin and NOACs: For warfarin, INR testing should be frequent for the first few weeks or months then normally every 1–2 months in AF⁶. This provides an opportunity to monitor adherence, effectiveness and safety. Self-monitoring of warfarin is an option. The level of anticoagulation with NOACs is not routinely measured*. • Access to a licensed product for rapid reversal of the anticoagulant effect: There is a licensed antidote for dabigatran etexilate (hospital prescribing only). Specific licensed antidotes for apixaban, edoxaban and rivaroxaban are not routinely available; clinical trials are ongoing. The anticoagulant effect of warfarin can be reversed using phytomenadione (vitamin K₁). • Experience: Warfarin has been used for more than 60 years, its short and long-term side

* 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 and rivaroxaban levels can be measured with a calibrated quantitative anti-factor Xa assay.

effect profiles are well-described.

- **Renal impairment:** Dose reduction (or sometimes avoidance) of NOACs is required (dabigatran etexilate, edoxaban and rivaroxaban – CrCl less than 50 ml/min⁷⁻⁹, apixaban – CrCl less than 30 ml/min¹⁰). Renal impairment is not a contraindication for warfarin use, although an increased frequency of INR monitoring is recommended. See [NICE CG182](#) for more information on anticoagulation in chronic kidney disease.
- **Extremes of BMI:** The relative dose of NOACs 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 effects¹¹. Changes in warfarin dosing may be required if patients lose or gain weight. See [warfarin SPC](#).
- **Risk of haemorrhage:** Where a centre (e.g. individual hospital) has INR TTR of ≤ 65%, NOACs 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%¹². NOACs are associated with a slightly higher risk of gastrointestinal haemorrhage¹².
- **Interactions:** Warfarin has many listed interactions. Careful INR monitoring can often prevent 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 first¹³.
NOACs have a number of listed interactions for which the advice is to avoid concomitant use (see eBNF¹⁴ and SPCs). Patients co-administered medication that may inhibit metabolism and potentiate bleeding risk with novel agents... are probably safer managed on warfarin as the INR may be adjusted accordingly¹¹.
- **Time in therapeutic range:** NOACs are likely to be more beneficial in patients whose INR on warfarin is regularly outside the therapeutic range despite good medication adherence¹¹. See also 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 NOAC as recommended. For AF, this is once a day (edoxaban or rivaroxaban) or twice a day (apixaban or dabigatran etexilate). The protective effect of the NOAC on the risk of stroke may fade 12–24 hours after a dose⁶.
- **Monitored dosage systems:** Dabigatran etexilate is not suitable for use in an adherence aid^{11†}.
- For people considering switching from warfarin, NOAC potential benefits should be considered against their potential risks, taking into account the person's level of INR control.
- **Diet:** Rivaroxaban should be taken with food.
Warfarin – Advise people to consume alcohol only within the recommended limits¹³.
Warfarin – Certain foods such as liver, broccoli, Brussels sprouts and green leafy vegetables contain large amounts of vitamin K. Sudden changes in diet, including cranberry juice, grapefruit juice, can potentially affect control of anticoagulation.

Those initiating warfarin or NOACs should have access to local resources on the use of these medicines e.g.:

- **Atrial Fibrillation Decision Support Tool** (www.anticoagulation-dst.co.uk/) – supports the majority of recommendations relating to the diagnosis and assessment of AF, assessment of stroke and bleeding risks and anticoagulation in the NICE guideline on AF. It also supports the contents of the NICE [patient decision aid for AF](#). This tool is for use with adults (aged 18 years and over) who have suspected or diagnosed non-valvular AF.
- [UKMi Common Questions and Answers on the Practical Use of Oral Anticoagulants in Non-Valvular Atrial Fibrillation](#).
- [AWMSG Risk-Benefit Assessment Tool for Oral Anticoagulant Treatment in People with Atrial Fibrillation](#)
- [AWMSG Summary - Assessment for All People Established on Oral Anticoagulation](#)
- [NICE Patient Decision Aid](#)
- [NOAC Monitoring Checklist](#).

Additional resources that may be of interest:

- [CKS Summary: Anticoagulation – oral](#) (AWMSG 2016)

	The prescriber should make efforts to understand and address the reasons for non-adherence before switching to an alternative medicine (AWMSG 2014).
3.4	NOACs may not be suitable for people with a history of poor adherence ¹¹ . Poor adherence to any oral anticoagulant regimen is likely to be associated with increased risk of thrombosis or bleeding (AWMSG 2014).
3.5	If poor anticoagulation control (see Recommendation 4.4) cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person (NICE 2014) ¹ .

[†] Not suitable for standard compliance aids; a specific dabigatran etexilate adherence aid can be provided.

3.6	<p>Ensure that people prescribed anticoagulants receive appropriate verbal and written information when necessary throughout the course of their treatment¹⁵ and are advised to carry an alert card with them at all times^{15,16}.</p> <p>People initiated on warfarin should be issued the information (yellow) booklet.</p> <p>People initiated on a NOAC should be provided with written information and monitoring booklet, e.g. the European Heart Rhythm Association (EHRA) Atrial Fibrillation Oral Anticoagulation Card.</p>
3.7	<p>In patients with AF the combination of aspirin and warfarin is not recommended¹³.</p> <p>If warfarin is indicated for moderate- or high-risk AF it should be used alone even in the presence of concomitant stable cardiovascular disease¹³.</p>
3.8	<p>Combination therapy of warfarin and antiplatelet may be advised by cardiologists, normally for a limited period, for patients who have coronary artery stents or cardiology intervention in the previous year. Clarification should be sought from the patient's interventional cardiologist if there is any doubt¹⁷.</p>
4.0	REVIEW
4.1	<p>Where warfarin is prescribed, there should be a documented process to systematically assess the TTR for each patient.</p> <p>Where NOACs are prescribed, there should be a documented process to systematically assess treatment (see UKMi Suggestions for Drug Monitoring in Adults in Primary Care). See also NICE QS 93 Statement 4 for suggested measures (AWMSG 2016).</p>
4.2	<p>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 (NICE 2014)¹ (see AWMSG Risk/Benefit Assessment Tool [2-page version]).</p>
4.3	<p>Undertake FBC, renal and liver function tests at least annually^{18,19} for people taking any anticoagulant. More frequent monitoring is advised if baseline tests are abnormal or there is intercurrent illness that may impact renal or hepatic function.</p>
4.4	<p>Reassess (see Recommendation 4.5) anticoagulation for a person with poor anticoagulation control shown by a TTR of less than 65% (NICE 2014)¹ over 6 months (see Recommendation 6.0). Consider also using the following as indicators of poor anticoagulation control:</p> <ul style="list-style-type: none"> • 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 (NICE 2014; AWMSG amendment 2016)
4.5	<p>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:</p> <ul style="list-style-type: none"> • 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 <p>Do not withhold anticoagulation solely because the person is at risk of having a fall (NICE 2014)¹. Useful tool: AWMSG Risk/Benefit Assessment Tool (2-page version).</p>
4.6	<p>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:</p> <ul style="list-style-type: none"> • diabetes • heart failure • peripheral arterial disease • coronary heart disease • stroke, transient ischaemic attack or systemic thromboembolism (NICE 2014)¹.
4.7	<p>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 (NICE 2014)¹.</p>
5.0	PRESCRIBING RESPONSIBILITY
5.1	<p>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.</p>
5.2	<p>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.</p> <p>If a primary care team does not have appropriate expertise to initiate warfarin 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.</p> <p>*Stabilisation: Two INR readings in range with confirmation that INR/dosing interval at least 7 days.</p>

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 general practice following a re-assessment of poor anticoagulant control to identify further possible causes.
5.4	In the hospital setting, the decision to start therapy with a NOAC 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 NOAC depending on health board service models.
5.5	The cause of an INR > 8 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: <ul style="list-style-type: none"> • Use a validated method of measurement such as the Rosendaal method for computer-assisted dosing, 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 (NICE 2014)¹.
6.2	Warfarin dosing: <ul style="list-style-type: none"> • Providers should normally use computer dosing software systems (AWMSG Warfarin Monitoring). • 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 (AWMSG 2014).
6.3	Self-monitoring of coagulation status in adults and children on long-term VKA therapy should be in accordance with NICE 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'.
7.0	REPORTING
7.1	Edoxaban and rivaroxaban are 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 www.yellowcard.gov.uk for definition of serious) to apixaban, dabigatran etexilate 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 www.yellowcard.gov.uk or cards available at the back of the British National Formulary (BNF) (AWMSG 2014).

Table 2. Recommendations on the Role of Warfarin for All Indications(See also [AWMSG Warfarin Monitoring](#))

8.0	MANAGEMENT OF SUPRATHERAPEUTIC INRs
8.1	People with mechanical valves with INR over 8 should be managed according to specialist advice.
8.2	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, who are being treated for AF, recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE). Exceptions: Recommendation 8.1 .
8.3	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 ¹⁴ . Expert opinion suggests that 2 mg is an adequate dose (AWMSG 2016). 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.
9.0	USE OF LOW MOLECULAR WEIGHT HEPARIN (LMWH) FOR SUBTHERAPEUTIC INR
9.1	Selected patients on warfarin who are at high risk of thromboembolism (for example, patients with mechanical valves or recurrent DVT/PE and those identified by the haematologist or cardiac surgeon) should be co-prescribed LMWH if the INR becomes sub-therapeutic (unlicensed indication). LMWH prescribing in these circumstances should be undertaken by the department responsible for dosing warfarin ²⁰ .

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