All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

All Wales Advice on the Role of Oral Anticoagulants

February 2016

This report 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. 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.

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.

2.2 Key sources

AWMSG guidance, NICE and NICE-accredited sources were used, including:

- AWMSG Advice on the Role of Oral Anticoagulants for the Prevention of Stroke and Systemic Embolism in People with Atrial Fibrillation
- Welsh Medicines Resource Centre Bulletin: Newer oral anticoagulants
- Scottish Intercollegiate Guidelines Network (SIGN) Prevention of stroke in patients with atrial fibrillation: a guide for primary care
- NICE CG180: Atrial Fibrillation
- SIGN 129. Antithrombotics: indications and management

2.2.1 Key policy documents, reports and national audits

- NHS Wales Delivery Framework 2013–2014 and Future Plans

2.2.2 Related national guidance

- NICE CG144: Venous thromboembolic diseases
- 1000 Lives Plus Improving Medicines Management – Reduction in INR > 5 and INR > 8 in hospital and community settings

2.3 Existing indicators and measures

2.3.1 2015/16 General Medical Services (GMS) contract Quality and Outcomes Framework (QOF)

2.3.2 Quality and Outcomes Framework Guidance for the GMS Contract Wales 2015/16

Atrial fibrillation (AF) Indicator	Points	Achievement thresholds
Records		
AF001. The contractor establishes and maintains a register of patients with atrial fibrillation	2	
Ongoing management		
AF006 The percentage of patients with atrial fibrillation in whom stroke risk has been assessed using CHA_2DS_2-VASc score risk stratification scoring system in the preceding 3 years (excluding those patients with a previous $CHADS_2$ or CHA_2DS_2-VASc score of 2 or more)	12	50-90%
AF007 In those patients with atrial fibrillation with a record of a CHA_2DS_2-VASc score of 2 or more, the percentage of patients who are currently treated with anticoagulation drug therapy	12	40-70%

2.3.3 NICE Quality Standard 93: AF 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

- EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation
- NICE CG182 Chronic kidney disease: assessment and management
- Greater Manchester Commissioning Support Unit: Prescriber Decision Support of New Oral Anti-Coagulants (NOACs)

For further information, see the AWMSG website: www.awmsg.org/.

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	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: • breathlessness/dyspnoea • palpitations • syncope/dizziness • chest discomfort • stroke/transient ischaemic attack (NICE 2014)[1].
1.2	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].
2.0	**INITIAL ASSESSMENT**
2.1	People with AF 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, using accredited decision aids where possible (e.g. NICE Patient Decision Aid) (AWMSG 2014).
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 AF management should be to identify affected people and undertake a stroke risk assessment using the CHA_2DS_2-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.
2.4	Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account (NICE 2014 Key Priority for Implementation [KPI])[1]. Consider anticoagulation for men with a CHA_2DS_2-VASc score of 1. Take the bleeding risk into account (NICE 2014)[1].
3.0	**CHOICE OF AGENT**
3.1	Do not offer aspirin monotherapy solely for stroke prevention to people with AF (NICE 2014 KPI)[1].
3.2	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]. 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. 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).
3.3	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 benefits[2–5]. In selecting the specific anticoagulant to use for the prevention of stroke and systemic embolism in people with non-valvular AF, consider: • **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 AF[6]. 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 K_1). • **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/min[7–9], apixaban – CrCl less than 30 ml/min[10]). 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 effects[11]. 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 haemorrhage[12]. • **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[13]. NOACs have a number of listed interactions for which the advice is to avoid concomitant use (see eBNF[14] 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 accordingly[11]. • **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 adherence[11]. 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 dose[6]. • **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 limits[13]. 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)
3.4	The prescriber should make efforts to understand and address the reasons for non-adherence before switching to an alternative medicine (AWMSG 2014). 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	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[15,16]. People initiated on warfarin should be issued the information (yellow) booklet. 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.
3.7	In patients with AF the combination of aspirin and warfarin is not recommended[13]. If warfarin is indicated for moderate- or high-risk AF it should be used alone even in the presence of concomitant stable cardiovascular disease[13].
3.8	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 doubt[17].
4.0	**REVIEW**
4.1	Where warfarin is prescribed, there should be a documented process to systematically assess the TTR for each patient. 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).
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 (NICE 2014)[1] (see AWMSG Risk/Benefit Assessment Tool [2-page version]).
4.3	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.
4.4	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: • 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	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 (NICE 2014)[1]. Useful tool: AWMSG Risk/Benefit Assessment Tool (2-page version).
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 • peripheral arterial disease • coronary heart disease • stroke, transient ischaemic attack or systemic thromboembolism (NICE 2014)[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 (NICE 2014)[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 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 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: • 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: • 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].

Table 3. Notes to accompany recommendations (2014; minor update 2016)

Recommendation	Notes
INITIAL ASSESSMENT	
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.	Baseline bleeding risk assessments have been an AWMSG recommendation since 2012[18] but are not consistently undertaken in all health boards. A systematic approach to baseline stroke and bleeding risk assessments is needed. This is a recommended audit measure.
2.3 The focus of AF management should be to identify affected people and undertake a stroke risk assessment using the CHA_2DS_2-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.	Patients who have a past history of haemorrhagic stroke and subsequently develop a new indication for anticoagulation, such as AF, should be assessed by a specialist, usually a stroke physician.
CHOICE OF AGENT	
3.2 Anticoagulation may be with warfarin or a 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]. *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.* *If, after using decision aids (such as NICE Patient Decision Aid and www.anticoagulation-dst.co.uk/), no preference exists, warfarin therapy (TTR over 65%) is a reasonable therapeutic option.*	Once the decision to initiate oral anticoagulation has been made, prompt access to therapy should be the priority. Health boards should ensure that local service models support prompt anticoagulation irrespective of anticoagulant choice. Particular consideration should be given to pathways supporting the effective anticoagulation for high-risk patients, such as those who have had a transient ischaemic attack and require rapid anticoagulation. Agreed update 2016.
3.3 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 benefits[2–5]. *In selecting the specific anticoagulant to use for the prevention of stroke and systemic embolism in people with non-valvular AF, consider:* • ***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 AF[6]. 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 $K_{1)}$.* • ***Experience**: Warfarin has been used for more than 60 years, its short and long-term side 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/min[7–9], apixaban – CrCl less than 30 ml/min[10]). 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*	Agreed update 2016.

[‡]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.

effects[11]. 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 haemorrhage[12].* • ***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[13].* *NOACs have a number of listed interactions for which the advice is to avoid concomitant use (see eBNF[14] 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 accordingly[11].* • ***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 adherence[11].* *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 dose[6].* • ***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 limits[13].* *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 AF* • *AWMSG Risk-Benefit Assessment Tool for Oral Anticoagulant Treatment in People with AF* • *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*	
Time in therapeutic range *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].*	The group considered: HAS-BLED TTR ≤ 60% and draft NICE ≤ 65% or range 60–65%. Members agreed to be consistent with NICE 2014: ≤ 65%.

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

Patient information *3.6 People initiated on a NOAC should be provided with written information and monitoring booklet, e.g. the EHRA Atrial Fibrillation Oral Anticoagulation Card.*	A standardised NHS Wales information sheet and log (modified from the Atrial Fibrillation Oral Anticoagulation Card) is under consideration.
REVIEW	
4.1 Where warfarin is prescribed, there should be a documented process to systematically assess the TTR for each patient. *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).*	**Background** **NICE CG 180 2014** 1.5.18 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. [new 2014] Calculate the person's TTR at each visit. When calculating TTR: • 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. **[new 2014]** **AWMSG 2014** Where warfarin is prescribed, TTR for each patient should be assessed at least annually[21]. CONSULTATION 2015 The feasibility of reviewing and taking action on a low TTR at every INR visit was considered. The AWMSG consultation draft proposed a pragmatic approach of quarterly review of TTRs to provide systematic identification of people with poor anticoagulation control. However, recent software improvements reporting TTR with each INR in both primary and secondary care suggest that processes are rapidly evolving in both settings and the updated wording allows for this. Anecdotal evidence suggests that people on NOACs may not be routinely reviewed or recalled and therefore UKMi guidance has been highlighted.
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 (NICE 2014)[1] (see AWMSG Risk/Benefit Assessment Tool [2-page version]).	Warfarin is dosed according to INR. For the newer agents the extent of anticoagulation is not routinely assayed and therefore no routine anticoagulant monitoring is required. However, for all anticoagulants, it is recommended that FBC, and renal and liver function tests are undertaken at least annually[19]. More frequent monitoring is advised if baseline tests are abnormal or there is intercurrent illness that may impact renal or hepatic function. New oral anticoagulants – 'Impaired renal function may constitute a contraindication or recommendation not to use the anticoagulant medicine, or may require a dose reduction; recommendations differ for the three medicines'[22].
PRESCRIBING RESPONSIBILITY	
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 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.*	[2014] There was moderate support for these recommendations.

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.*	The statement has been updated to reflect the increased experience in use of newer agents and increased availability of independent decision aids. The NICE Patient Decision Aid supports patients in the decision about whether to start an anticoagulant based on their preferences, and personal stroke and bleeding risk profile. It includes tables outlining the implications of warfarin versus NOAC therapy. It does not include information on individual NOACs (the NICE Patient Decision Aid can be accessed here: www.nice.org.uk/guidance/cg180/resources/).
MONITORING OF INR CONTROL (WARFARIN ONLY)	
Warfarin stabilisation *6.1 When calculating TTR:* • *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].*	When considering the analysis of TTR, AWMSG 2012 stated, "TTR should not be assessed within the initiation period (normally 1–3 months)". This statement was updated [2014] to 6 weeks, to reflect NICE 2014[1]. Whilst there is pressure on warfarin clinics, it is important that a patient is sufficiently stabilised on warfarin to ensure that they understand the monitoring requirements and that dosing information can be safely communicated.
REPORTING	
INR over 8 – clinical governance	It is thought that most health boards investigate and report INRs over 8. There is uncertainty regarding the collation of reports, feedback to prescribers or subsequent organisational learning. It is recommended that the clinical governance arrangements for INRs over 8 are investigated further and promoted. The NICE Implementation Collaborative 'Supporting local implementation of NICE guidance on use of the novel (non-VKA) oral anticoagulants in non-valvular AF' states that local protocols should be available on management of bleeding in patients taking oral anticoagulants[23].
Audit and collation of adverse events *7.1 Edoxaban and rivaroxaban are currently under 'Additional Monitoring' by the EMA and all suspected 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 MHRA through the Yellow Card Scheme using the electronic form at www.yellowcard.gov.uk or cards available at the back of the BNF (AWMSG 2014).*	2014: Subgroup discussed the All Wales Risk/Benefit Assessment Tool and the opportunity to undertake national data collection. NICE CG180 makes the research recommendation: Do people with AF whose anticoagulant control is poor, or is predicted to be poor, with warfarin benefit from changing to one of the NOACs?[1] Collation of data is undertaken in several localities in addition to the Royal College of Physicians' S44Tentinel Stroke National Audit Programme (44TSSNAP). It is recommended that members collaborate to develop an agreed core data set.
MANAGEMENT OF SUPRATHERAPEUTIC INRs	
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.*	Amended to be consistent with the Wales anticoagulation drug chart.

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