Pathway for the prevention of stroke and systemic embolism in non – valvular atrial fibrillation

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July 2017

(Review date July 2020)

Version control

Version Number	Amendments made	Author	Date
1	N/A	Sharon Andrew	20/9/17
1.1	Addition of Guidelines for Antiplatelet/Anticoagulant Therapy for Primary and Secondary Prevention of Ischaemic Stroke and Transient Ischaemic Attack (TIA) as appendix 1	Sharon Andrew	16/7/18
Date of next review: September 2020			

Contents

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is a major cause of ischaemic stroke. Anticoagulation to reduce the risk of stroke is an essential part of AF management but patients are not always appropriately anticoagulated. NICE Guidance emphasises the importance of undertaking a stroke risk assessment for all patients with AF and anticoagulating, where safe and appropriate. All people with AF should be offered a personalised package of care which includes up-to-date, comprehensive information and practical advice on their anticoagulation in line with recommendations made in NICE CG144[i] section 1.3.1. and NICE CG 180[ii] section 1.2.

Background

Estimates suggest that the prevalence of AF is increasing. The Health and Social Care Information Centre's 2011–12 Quality and outcomes framework estimated the prevalence of known atrial fibrillation to be 1.57%. The NHS Improving Quality Guidance on risk assessment and stroke prevention for atrial fibrillation (GRASP-AF) tool estimated the prevalence to be between 1.65% and 1.76%. However, it has been shown that the true prevalence of atrial fibrillation is underestimated and could be around 2.0% (Hobbs et al. [2005] A randomised controlled trial and cost-effectiveness study of systematic screening [targeted and total population screening] versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. Health Technology Assessment 40: 1–74).

The management of atrial fibrillation should aim to prevent complications, particularly stroke, and alleviate symptoms.

The more recent availability of Direct Oral Anticoagulants (DOACs), has led to a major change in the management of stroke prevention in atrial fibrillation (AF). At the same time there is greater understanding of how to manage warfarin, with the importance of the average time in therapeutic range (TTR) increasingly recognised.

Currently, within Lancashire there is no uniform AF patient journey / treatment pathway across the 8 CCGs leading to potential disparity in:

- How a patient is diagnosed with AF
- Interventions to prevent stroke
- Assessment of anticoagulation control with Vitamin K antagonists
- Patient review

The NICE quality standard for atrial fibrillation: treatment and management (QS 93)[iii] specifies that services should be commissioned from and coordinated across all relevant agencies encompassing the whole atrial fibrillation care pathway. A person-centred, integrated approach to providing services is fundamental to delivering high-quality care to adults with atrial fibrillation.

A single streamlined patient pathway covering diagnosis, assessment, induction, monitoring and review would in theory provide a much more cost effective, high quality approach whilst reducing disparity and the potential associated risks.

These might include high risk patients not being identified, high risk patients not being offered anticoagulation and patients who do not maintain adequate TTRs being unidentified.

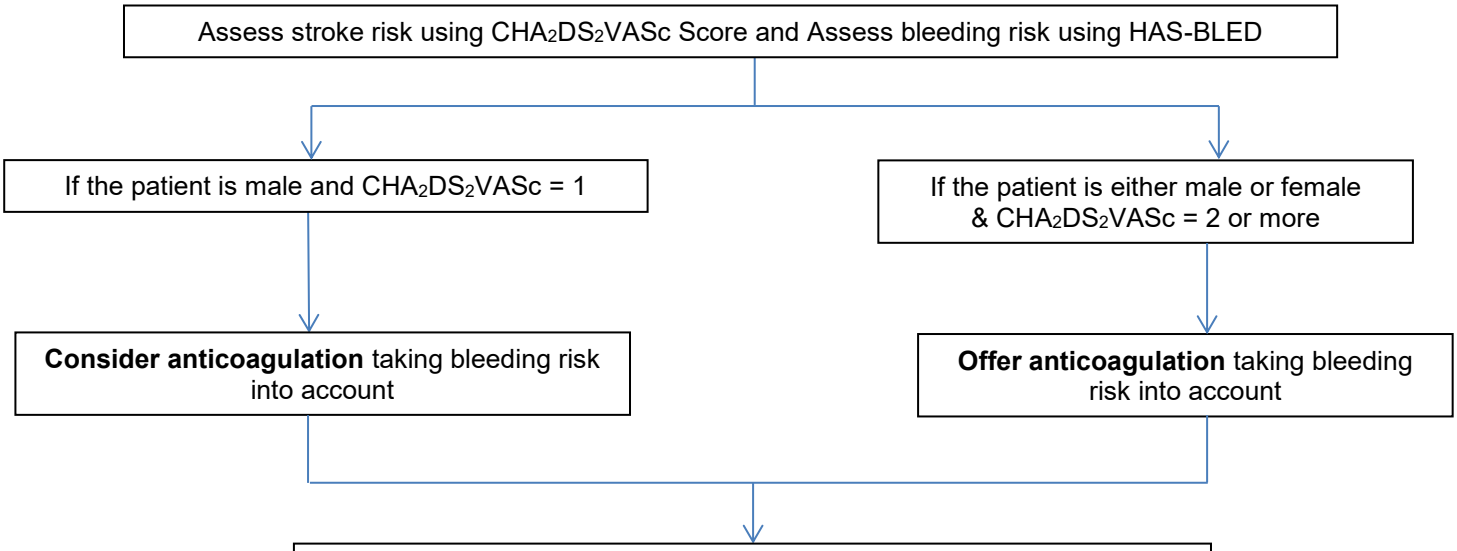
Due to the changing landscape in available anticoagulation it is important to consider whether people with atrial fibrillation whose anticoagulant control is poor, or is predicted to be poor with warfarin, benefit from changing to one of the non-vitamin K antagonist (non-VKA) oral anticoagulants.

Trials of the non-VKA oral anticoagulants have shown that the degree of benefit of these agents compared with warfarin may depend on the time in therapeutic range (TTR) of the warfarin group. These trials assessed the degree of benefit in relation to the mean TTR for the warfarin group in that country.

However, the inference of benefit is based on a number of assumptions. It is unclear that the population TTR can be extrapolated to decision-making in an individual. If, for example, an individual's low TTR is a result of poor compliance, it is unlikely that compliance will improve with a non-VKA oral anticoagulant and it is uncertain whether a non-VKA oral anticoagulant will offer any benefit. Moreover, the threshold of TTR at which a non-VKA oral anticoagulant might offer benefit is unclear. The same question can be extended to include people before they start warfarin treatment, using criteria that prospectively identify those likely to have poor control on warfarin (NICE CG180)[ii].

This guidance does not override the individual responsibility of health professionals to make decisions in exercising their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. For full prescribing information please refer to the BNF and SPC ensuring correct SPC according to dose is consulted.

Assessment of Patient: CHA2DS2VASc and HAS-BLED



Discuss the risks & benefits of each stroke prevention strategy. Choice of anticoagulant should be based on clinical features & patient preference.

Warfarin is the most cost effective and may be the preferred option for those people with AF:

- Who are currently well controlled on warfarin
- Who have never taken an anticoagulant (after discussing risks and benefits with the patient)
- Who are at risk of drug interactions with a novel oral anticoagulant
- Who have a CrCl (eGFR) <30 ml/min/1.73m^2
- Who have no additional risk factors

NOACs may be the preferred option for people with AF:

- Who are not taking warfarin because of allergy or intolerance, or in circumstances where routine INR monitoring may be impractical (provided that monitoring of renal and liver function is still practicable)
- Who are currently taking warfarin but, despite evidence of good compliance with medication and monitoring, have poor anticoagulant control
- Who are at risk of drug interactions with warfarin

NB: **Warfarin** has been used for over 60 years and has the advantages of allowing compliance to be measurable. In the case of major bleeding, anticoagulation can be reversed. Whilst NOACs do not need INR monitoring, careful initiation and management is essential. There is no standard measure to assess compliance with NOACs and, as they have a relatively short half-life, compliance is critical as protection from stroke will be lost with omission of only one dose (in contrast to warfarin). Currently only dabigatran has an established antidote**.**

If poor control is because of non- compliance, switching to a different agent is unlikely to address the issue.

Anticoagulant Choice

NICE guidance states that the decision to start treatment with a DOAC should be made after an informed discussion between the clinician and the patient about the risks and benefits of warfarin compared with DOACs.

Local Recommendation:

Consider apixaban, dabigatran, edoxaban or rivaroxaban for the following groups of NVAF patients at high risk of stroke (e.g. CHADS2 or CHA2DS2VASc score ≥1):

- Not able or prepared to take warfarin after informed consideration.
- Poor INR control with warfarin despite good compliance.
- Suffered a stroke or systemic embolism whilst on warfarin despite good compliance.
- On multiple drug therapy with high risk of warfarin drug interactions.
- Taking regular blood samples presents a practical problem.
- Initiation by specialists for NVAF patients requiring rapid INR control.

NVAF patients that can be well controlled on warfarin (i.e. Time in INR Treatment Range / TTR more than or equal to 65%) **are not locally recommended as priority candidates for the use of DOACs**.

In these patients, the potential advantages of the DOACs vs warfarin are debateable. Therefore, the local recommendation is to adopt a cautious approach to the prescribing of this newer class of oral anticoagulants, whilst also supporting informed patient decision making.

NB: Good medication compliance is as important with the DOACs as it is with warfarin, as missing a dose, or overdoses, will also have significant efficacy or safety implications.

Additional Information

- Reinforcing the bleeding risks associated with DOACs to patients will be important, to avoid patients becoming complacent with their anticoagulant dosing in the absence of the need for regular monitoring blood tests.
- The efficacy and safety of the DOACs in people in whom warfarin is relatively or absolutely contraindicated, has not been conclusively established.
- The long term safety or effectiveness data for the DOACs is still developing. Warfarin has more than 50 years of accumulated clinical experience.
- Rivaroxaban, edoxaban and warfarin are taken **once** daily. Dabigatran and apixaban are **twice** daily.
- Rivaroxaban and apixaban (but NOT dabigatran) can be dispensed in standard monitored dosage system (MDS) compliance aids such as dosset boxes. (Special MDS containers are required for dabigatran capsules as they are moisture sensitive).
- The NICE AF guidance (June 2014) no longer recommends the use of aspirin to prevent thromboembolic events in people with AF. People taking aspirin solely for this indication should be reviewed as a matter of priority.
- Patients should be advised to carry an appropriate anticoagulant alert card.

NICE Criteria for Warfarin / DOAC initiation

	Warfarin (CG 180)	Apixaban (TA275 & CG180)[iv,ii]	Dabigatran (TA249 & CG180)[v,ii]	Edoxaban (TA355)[vi]	Rivaroxaban (TA256 & CG180)[vii,ii]
NICE Criteria	**N/A** **NO** additional risk factors need to be present	Recommended as an option in people with nonvalvular atrial fibrillation with ≥1 risk factors such as: •prior stroke or transient ischaemic attack •age ≥75 years •hypertension •diabetes mellitus •symptomatic heart failure (≥New York Heart Association class 2)	Recommended as an option in people with nonvalvular atrial fibrillation with≥ 1 of the following risk factors: •previous stroke, transient ischaemic attack or systemic embolism •age≥ 75 years •symptomatic heart failure (≥New York Heart Association class 2) •left ventricular ejection fraction below 40% •age≥ 65 years with one of the following: diabetes mellitus, coronary artery disease or hypertension.	Recommended as an option in adults with nonvalvular atrial fibrillation with≥ 1 risk factors including: •prior stroke or transient ischaemic attack •age ≥75 years •hypertension •diabetes •congestive heart failure	Recommended as an option in people with nonvalvular atrial fibrillation with ≥1 risk factors such as: •prior stroke or transient ischaemic attack. •age ≥75 years •hypertension •diabetes mellitus •congestive heart failure

Cautions: DOACs – renal impairment, age, weight

Normal Adult Dose	Reduced Dose	Contraindication
Apixaban 5mg bd	Dose reduction to 2.5mg bd required if: CrCl 15-29 ml/min **or** if at least two of the following : age ≥ 80 years; body weight, ≤ 60 kg; or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).	Contraindicated if CrCl <15ml/min
Dabigatran 150mg bd	Dose reduction to 110mg bd required if: CrCl 30-50 ml/min and at high risk of bleeding **or** if >80 years	Contraindicated if CrCl <30 ml/min
Edoxaban 60mg od	Dose reduction to 30mg daily required if: CrCl 15-50 ml/min **or** weight < 60kg	Contraindicated if CrCl <15 ml/min **or** on dialysis
Rivaroxaban 20mg od	Dose reduction to 15mg daily required if: CrCl 15-49 ml/min	Contraindicated if CrCl <15 ml/min

NB: With Edoxaban there is a trend towards decreasing efficacy with increasing CrCl, therefore only use in patients with high CrCl after evaluation of the individual thromboembolic and bleeding risk

With all the DOACs drug accumulation can occur with impaired renal function.

- Renal function should be checked prior to initiation and monitored when necessary e.g. when other drugs with renal effects are introduced or with dehydration/vomiting/ diarrhoea.
- Renal function should be monitored at least annually.
- Liver function should be checked prior to initiating apixaban.

References

i Venous thromboembolic diseases: diagnosis, management and thrombophilia testing Clinical guideline [CG144] Published date: June 2012 Last updated: November 2015 https://www.nice.org.uk/guidance/cg144/chapter/Recommendations#patient-information

ii Atrial fibrillation: management Clinical guideline [CG180] Published date: June 2014 Last updated: August 2014 https://www.nice.org.uk/guidance/cg180/chapter/1-Recommendations#personalised-package-of-care-and-information-2

iii Atrial fibrillation Quality standard [QS93] Published date: July 2015 https://www.nice.org.uk/guidance/qs93

iv Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation Technology appraisal guidance [TA275] Published date: 27 February 2013 https://www.nice.org.uk/guidance/ta275

v Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation Technology appraisal guidance [TA249] Published date: 15 March 2012 https://www.nice.org.uk/guidance/ta249

vi Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation Technology appraisal guidance [TA355] Published date: 23 September 2015 https://www.nice.org.uk/guidance/ta355

vii Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation Technology appraisal guidance [TA256] Published date: 23 May 2012 https://www.nice.org.uk/guidance/ta256

Appendix 1
Guidelines for Antiplatelet/Anticoagulant Therapy for Primary and Secondary Prevention of Ischaemic Stroke and Transient Ischaemic Attack (TIA)

Patient with no history of Atrial Fibrillation (AF)

Primary Prevention

i.e. No previous history of cardiovascular disease

Do not routinely prescribe antiplatelet treatment.[1]

See Page 2 for further Information

Consider other stroke prevention strategies

e.g. Lipid modification, BP management, smoking cessation and diabetes control.

See Page 2 for further Information

Secondary Prevention

Of occlusive vascular event following ischaemic stroke or TIA

1st Line: Clopidogrel 75mg once daily *

OR (if clopidogrel is contraindicated or not tolerated)

2nd Line: Aspirin 75mg (dispersible tablet) once daily after food + dipyridamole 200mg MR capsule one twice daily after food

OR (if both clopidogrel and dipyridamole are contraindicated or not tolerated)

3rd Line: Aspirin 75mg daily after food alone

OR (if aspirin and clopidogrel are contraindicated or not tolerated)

4th Line: Dipyridamole MR 200mg capsule one twice daily alone after food[3]

Patient with a history of non-valvular Atrial Fibrillation (AF)

See LMMG Pathway for the prevention of stroke and systemic embolism in non – valvular atrial fibrillation

1. Assess stroke risk using CHA_2DS_2-VASc
2. Assess bleeding risk using HAS-BLED – modify and monitor risk factors, where appropriate
3. Consider anticoagulation for males with a CHA2DS2VASc score of 1 (take bleeding risk into account).
4. Offer anticoagulation to males & females with CHA2DS2VASc score ≥ 2 (take bleeding risk into account).
5. If, on discussion, anticoagulation is rejected because of bleeding risks or other factors review the decision annually & document the reasoning.
6. Do NOT offer aspirin monotherapy solely for stroke prevention in AF. For patients currently taking aspirin, consider anticoagulation, taking account of co-morbidities & other reasons for using aspirin.
7. Stop aspirin if being prescribed solely as monotherapy for stroke prevention for AF patients as per NICE QS93. The risks of taking aspirin outweigh any benefits of taking it as monotherapy for stroke prevention in adults with atrial fibrillation.[4]
8. The decision about which oral anticoagulant to start should be based on the patients clinical features & preferences. There should be an informed discussion between the clinician & patient, with consideration of the risks & benefits of different therapies.

*Secondary prevention of TIA is not a licensed indication of clopidogrel 75mg tablets and for this reason is not recommended by NICE TA210. However LMMG and the Royal College of Physicians Intercollegiate Stroke Working Party National Clinical Guidelines For Stoke recommend clopidogrel first line for this indication.[5]

Antiplatelet Treatment for Primary Prevention of Cardiovascular Events

Use of aspirin in primary prevention of cardiovascular events (off-label), in patients with or without diabetes, is of unproven benefit and routine use is not recommended.[1]

NICE NG17 states do not offer aspirin for the primary prevention of cardiovascular disease to adults with type 1 diabetes.[6]

Expert opinion is conflicting for further information on use in other patient groups see http://cks.nice.org.uk/antiplatelet-treatment#!scenario .[2]

Management of Patients with non-valvular AF and Cardiovascular Disease

AF and stable vascular disease (i.e. no acute events or revascularization for >12 months, whether coronary or peripheral artery disease):

- The European Society of Cardiology ESC guidelines for the management of AF recommend that patients with stable vascular disease can be managed with OAC alone. In such stable patients, there is no need for concomitant aspirin, which could increase the risk of serious haemorrhage, including intracranial haemorrhage.[7]

AF and unstable cardiovascular disease (Acute Coronary Syndrome and/or PCI/stent procedure in the preceding year):

- It is expected that a cardiologist will advise on the most appropriate treatment strategy for this patient group.
- Data on triple therapy with oral anticoagulants (OACs) (when given at stroke prevention doses in AF patients) are limited. ESC Guidelines based on expert consensus opinion recommend a period of triple therapy is needed (OAC plus aspirin plus clopidogrel), followed by the combination: OAC plus single antiplatelet drug. After one year, management can be with OAC alone in stable patients. Combination therapy with any OAC and antiplatelets significantly increases the risk of bleeding.[7]

Other Stroke Prevention Strategies

In addition to the use of antiplatelets/anticoagulation for the primary and secondary prevention of stroke/TIA, other risk management strategies should also be considered e.g. Blood Pressure management, lipid modification, control of diabetes and lifestyle interventions:

- NICE CG 181 [8] (July 2014 / updated September 2016) Cardiovascular disease: risk assessment and reduction, including lipid modification covers lifestyle modifications as well as lipid modifications for the primary and secondary prevention of CVD
- Lifestyle advice and further drug treatments (including statins and BP management) for secondary prevention of stroke/TIA is available from NICE CKS [9]

References

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4. National Institute for Health and Care Excellence Atrial Fibrillation: Treatment and Management Quality Standard 93 2015 http://www.nice.org.uk/guidance/QS93/chapter/Quality-statement-2-Use-of-aspirin
5. Royal College of Physicians Intercollegiate Stroke Working Party (RCP ISWP); *National clinical guideline for stroke* https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx accessed 1/3/18
6. National Institute for Health and Care Excellence *Type 1 Diabetes in Adults: Diagnosis and Management* NICE Guideline 17 2015 http://www.nice.org.uk/guidance/ng17/resources/type-1-diabetes-in-adults-diagnosis-and-management-1837276469701 accessed 1/3/18
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8. National Institute for Health and Care Excellence Cardiovascular disease: risk assessment and reduction, including lipid modification CG181 https://www.nice.org.uk/guidance/cg181 accessed 1/3/18
9. National Institute for Health and Care Excellence Clinical Knowledge Summary Stroke and TIA http://cks.nice.org.uk/stroke-and-tia#!topicsummary accessed 1/3/18