

## Prevention of stroke in patients with atrial fibrillation

*A guide for primary care*

*January 2014*

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# 1 Introduction

Atrial fibrillation (AF) is a common and serious condition, affecting at least 1.8% of the population, rising to over 6% in people aged over 65 years. As the population ages, prevalence is increasing. People with AF are five times more likely to have a stroke and have an increased risk of premature death, resulting in enormous personal, social and economic cost. Prevention of stroke is the main aim of management of AF. AF is under-diagnosed and the use of oral anticoagulants (OACs) is inadequate. There is an urgent need to improve diagnosis and to encourage better uptake and adherence to oral anticoagulation drugs (Royal College of Physicians of Edinburgh (RCPE) Consensus Conference, 2012 [www.rcpe.ac.uk/sites/default/files/files/Final\\_statement.pdf](http://www.rcpe.ac.uk/sites/default/files/files/Final_statement.pdf)).

This guide summarises the current evidence available to support the management of AF in primary care.

The guide was developed by Healthcare Improvement Scotland by collating existing recent advice and guidance, including evidence based guidelines and consensus recommendations for practice in NHSScotland. An **expert group** reviewed the draft guide.

## 2 Detection

There are no Scottish evidence based guidelines on the detection of atrial fibrillation. The 2012 RCPE Consensus Conference made the following recommendations for detection of AF:

- The most cost-effective method for the detection of AF in primary care is by opportunistic screening of people aged 65 years or older by radial pulse checking followed as soon as practicable by a 12-lead electrocardiogram (ECG) for those with an irregular pulse.
- Use of a single lead ECG recording at the time of symptoms can help in diagnosis but does not replace the need for a 12-lead ECG.
- Diagnostic ECGs should be analysed by a competent individual supported by audit and feedback.
- Where clinical suspicion of paroxysmal AF exists, including after ischaemic stroke or transient ischaemic attack (TIA), longer ECG monitoring periods (at least 24 hours) or event recorders should be used.

## 3 Risk stratification

SIGN 129 Antithrombotics: indications and management, published in June 2013 ([www.sign.ac.uk/pdf/SIGN129.pdf](http://www.sign.ac.uk/pdf/SIGN129.pdf)), provides evidence for assessing risk of stroke in patients with AF.

A meta-analysis of seven studies shows prior stroke/TIA, advancing age, hypertension and diabetes to be associated with risk of stroke in patients with atrial fibrillation, with prior stroke conferring the highest risk. In light of these factors several schemes for stratification of stroke risk have been proposed. The CHADS<sub>2</sub> (Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus and prior Stroke or transient ischaemic attack) score has been validated (Table 1).

More detailed stroke risk assessment can be achieved by inclusion of additional risk factors. In CHA<sub>2</sub>DS<sub>2</sub>-VASc two points are allocated for the 'major risk factors' of a history of stroke or TIA, and for age >75 years (Table 2). Using this scheme in a patient cohort with atrial fibrillation there was an increasing stroke rate with increasing scores (Table 3).

**SIGN 129 makes the following recommendations on risk stratification:**

- D** In all patients with AF, risk factors for systemic thromboembolism should be assessed routinely using CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score.
- B** Patients with AF who are clearly low risk, (age<65 and lone AF) do not require antithrombotic therapy. This applies to male patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score=0 and female patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score=1 in whom the single point is allocated due to female sex.

Table 1: CHADS<sub>2</sub> scoring

CHADS <sub>2</sub> risk factor	Score
Heart failure	1
Hypertension	1
Age >75 years	1
Diabetes mellitus	1
Prior stroke/TIA	2

Table 2: CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring

CHA <sub>2</sub> DS <sub>2</sub> -VASc scoring	Score
Congestive heart failure (inc Left Ventricular Dysfunction)	1
Hypertension	1
Aged 75 or more	2
Diabetes	1
Stroke/TIA/thromboembolism	2
Vascular disease (prior Myocardial Infarction, Peripheral Artery Disease or aortic plaque)	1
Aged 65-74	1
Sex category: female	1

Table 3: Annual stroke rate associated with CHADS<sub>2</sub> risk scores

Risk	CHADS <sub>2</sub> score	Annual stroke rate (%)
LOW	0	1.9
INTERMEDIATE	1	2.8
		4.0
HIGH	3	5.9
	4	8.5
	5	12.5
	6	18.2

## 4 Treatment to prevent stroke in patients with atrial fibrillation

SIGN 129 Antithrombotics: indications and management, published in June 2013 ([www.sign.ac.uk/pdf/SIGN129.pdf](http://www.sign.ac.uk/pdf/SIGN129.pdf)), provides evidence for treatment for prevention of stroke in patients with AF.

### WARFARIN

In a meta-analysis which included five trials and 2,313 patients with a mean age of 69 years who were followed up for a mean of 1.5 years, dose-adjusted warfarin leading to an international normalised ratio (INR) of between 2.0 and 3.0 reduced stroke rates in patients with non-valvular AF, odds ratio (OR) 0.34 (95% confidence interval (CI) 0.23 to 0.52) with wide confidence intervals for rates of extra- and intracranial haemorrhages.

A meta-analysis of eight trials and 9,598 patients compared dose-adjusted Vitamin K antagonist (VKA), mainly warfarin to platelet inhibitor, mainly aspirin alone, for patients in AF with no history of stroke or TIA, with a mean follow-up of 1.9 years. A dose-adjusted VKA was associated with a lower risk of stroke than platelet inhibitor, OR 0.68 (95% CI 0.54 to 0.85).

A further meta-analysis compared 29 trials, 28,044 patients, with a mean age of 71 years. This showed that dose-adjusted warfarin reduced stroke by 60% compared to 20% with antiplatelet agents in patients with non-valvular AF. The absolute increase in major extracranial haemorrhage was 0.2% per year with warfarin compared with aspirin, less than the absolute reduction in risk of a first stroke (0.7% per year).

Despite its superiority in preventing embolic events in patients with AF, it has been shown that warfarin is underused in these patients.

Warfarin use has generally been limited in the elderly by concerns over falls and risks of haemorrhage. A randomised controlled trial (RCT) comparing 485 patients taking 75 mg aspirin and 488 patients taking dose-controlled warfarin with an INR of 2.0-3.0 who were followed up for a mean of 2.7 years showed that warfarin is better than aspirin at stroke prevention in patients with AF aged over 75 years (risk reduction (RR) 0.48, 95% CI 0.28 to 0.80,  $p=0.003$ ; absolute yearly risk reduction 2%, 95% CI 0.7 to 3.2). Risks of major extracranial haemorrhage were similar at 1.4% with warfarin and 1.6% with aspirin.

Contraindications to warfarin include increased risk of bleeding. A systematic review investigating risk factors for bleeding included nine studies. Advancing age, uncontrolled hypertension, history of myocardial infarction (MI) or ischaemic heart disease (IHD)/cerebrovascular disease, anaemia, a history of bleeding and concomitant use of other drugs which predispose to bleeding were all identified as risk factors for anticoagulation-related bleeding.

## COMBINATION THERAPY WITH ASPIRIN AND WARFARIN

The combination of aspirin and warfarin in patients with chronic atrial fibrillation alone or with concomitant coronary artery disease (CAD) does not reduce the risk of arterial thromboembolism compared with those on oral anticoagulant therapy alone but increases the risk for major bleeding.

## DABIGATRAN ETEXILATE

In a large, randomised non-inferiority trial with blinded adjudication of events, the orally active direct thrombin inhibitor dabigatran etexilate was compared to warfarin in patients with AF and at increased risk of stroke. At a dabigatran dose of 110 mg twice daily, efficacy in prevention of vascular events was comparable to warfarin but major bleeding was less frequent (2.87% versus 3.57%,  $p=0.002$ ). At a dose of 150 mg twice daily, stroke and systemic embolism occurred significantly less frequently than with warfarin (1.11% per year versus 1.69% per year, RR 0.66; 95% CI 0.53 to 0.82,  $p<0.001$ ) with similar rates of major haemorrhage (3.31% versus 3.57%,  $p=0.32$ ).

One RCT involving 18,113 patients showed that in centres where INR control was very good or excellent, warfarin performed as well as, if not better than, dabigatran in terms of stroke risk reduction and bleeding events.

## RIVAROXABAN

In one RCT rivaroxaban was compared to warfarin in patients with AF at increased risk of stroke. For the primary outcome of stroke or systemic embolism there were 1.7% per year in the rivaroxaban group and 2.2% per year in the warfarin group (hazard ratio (HR) 0.79, 95% CI 0.66 to 0.96,  $p<0.001$  for non-inferiority). There was no significant difference in major bleeding.

## APIXABAN

Apixaban was compared with aspirin in an RCT of stroke prevention in patients with AF at increased risk of stroke and in whom VKA therapy was deemed to be unsuitable. The trial was stopped early due to a clear benefit of apixaban: stroke or systemic embolism occurred at 1.6% per year in those randomised to apixaban and 3.7% per year in the aspirin group. Rates of major bleeding were not significantly different between groups.

In a further RCT apixaban was shown to be superior to warfarin in preventing stroke or systemic embolism, caused less bleeding and resulted in lower mortality in patients with AF and at least one additional risk factor for stroke. The rate of the primary outcome (ischaemic or haemorrhagic stroke or systemic embolism) was 1.27% per year compared with 1.65% per year for warfarin (HR 0.79, 95% CI 0.66 to 0.95,  $p=0.01$  for superiority). The event rate for major or clinically relevant non-major bleeding was 4.07% per year in the group receiving apixaban compared with 6.01% per year in the group receiving warfarin (HR 0.68, 95% CI 0.61 to 0.75,  $p<0.001$ ).



**SIGN 129 makes the following recommendations on treatment:**

- A** All patients with AF who have a CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 1$  (one or more clinically relevant risk factors) should be considered for warfarin at a target INR of 2.5 (range 2.0-3.0) or a newer anticoagulant. The balance of risks and benefits of anticoagulant therapy should be assessed and discussed annually with the patient, with consideration given to patient preference.
- A** Antiplatelet therapy should only be considered where warfarin or one of the alternative new anticoagulants has been declined.
- A**
  - In patients with AF the combination of aspirin and warfarin is not recommended.
  - If warfarin is indicated for moderate- or high-risk AF it should be used alone even in the presence of concomitant stable cardiovascular disease.
- A** Dabigatran etexilate can be considered as an alternative to warfarin in the management of patients with atrial fibrillation with one or more risk factors for stroke.
- A** Rivaroxaban can be considered as an alternative to warfarin in the management of patients with atrial fibrillation with one or more risk factors for stroke.
- A** Apixaban can be considered as an alternative to warfarin in the management of patients with atrial fibrillation with one or more risk factors for stroke.
- ✓** In selecting a novel antithrombotic consideration should be given to:
  - the relative lack of experience of long term use compared with a VKA or aspirin
  - the lack of a licensed product for rapid reversal of the anticoagulant effect
  - the limited data on use in patients at the extremes of body weight and those with hepatic impairment.

## 5 Supporting safe and effective use of oral anticoagulants

In August 2012 Healthcare Improvement Scotland published an implementation statement to support the safe and effective use of dabigatran and rivaroxaban in NHSScotland ([www.healthcareimprovementscotland.org/our\\_work/cardiovascular\\_disease/stroke\\_and\\_systemic\\_embolism/stroke\\_and\\_systemic\\_embolism.aspx](http://www.healthcareimprovementscotland.org/our_work/cardiovascular_disease/stroke_and_systemic_embolism/stroke_and_systemic_embolism.aspx)).

It should be noted that the statement was developed and issued prior to the licensing and subsequent Scottish Medicines Consortium (SMC) approval of apixiban.

**The implementation statement makes the following recommendation:**

- on balance of risks and benefits, warfarin remains the anticoagulant of clinical choice for moderate or high risk atrial fibrillation patients ( $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ ) with good INR control.

# 6 Sources of further information

## USEFUL PUBLICATIONS

### Atrial Fibrillation

[www.bhf.org.uk/publications/view-publication.aspx?ps=1000952](http://www.bhf.org.uk/publications/view-publication.aspx?ps=1000952)

[www.bcpa.co.uk/factsheets/AtrialFibrillation.htm](http://www.bcpa.co.uk/factsheets/AtrialFibrillation.htm)

### Understanding Atrial Fibrillation

[www.chss.org.uk/publications/documents/Heart/H9\\_Atrial\\_Fibrillation\\_web.pdf](http://www.chss.org.uk/publications/documents/Heart/H9_Atrial_Fibrillation_web.pdf)

### Warfarin

[www.chss.org.uk/publications/documents/factsheets/F4\\_Warfarin.pdf](http://www.chss.org.uk/publications/documents/factsheets/F4_Warfarin.pdf)

## ORGANISATIONS

### AntiCoagulation Europe

PO Box 405, Bromley, Kent BR2 9WP

Phone: 020 8289 6875

E-mail: [admin@anticoagulationeurope.org](mailto:admin@anticoagulationeurope.org)

Website: [www.anticoagulationeurope.org](http://www.anticoagulationeurope.org)

AntiCoagulation Europe is a UK charity providing information, education and support to patients and their families. A range of information including short videos is available on their website on topics such as self-testing and self-management.

### Atrial Fibrillation Association

PO Box 1219, Chew Magna, Bristol BS40 8WB

Phone: 01789 451837

Email: [info@atrial-fibrillation.org.uk](mailto:info@atrial-fibrillation.org.uk)

Website: [www.atrialfibrillation.org.uk](http://www.atrialfibrillation.org.uk)

The Atrial Fibrillation Association is an international charity providing information and support to patients who have atrial fibrillation.

### British Cardiac Patients Association

15 Abbey Road, Bingham, Nottingham NG13 8EE

Phone: 01949 837070

National Helpline 01223 846845

Email: [Admin@BCPA.co.uk](mailto:Admin@BCPA.co.uk)

Website: [www.bcpa.co.uk](http://www.bcpa.co.uk)

The British Cardiac Patients Association is a charitable organisation run by volunteers providing support, advice and information to cardiac patients and their carers.

### **British Heart Foundation (Scotland)**

Ocean Point, 194 Ocean Drive, Edinburgh EH6 6JH

Phone: 0131 555 5891

Heart Helpline 0300 330 3311 (available Mon-Fri 9am-5pm)

Email: [scotland@bhf.org.uk](mailto:scotland@bhf.org.uk)

Website: [www.bhf.org.uk](http://www.bhf.org.uk)

The British Heart Foundation provides a free telephone information service for those seeking information on heart health issues. Also provides a range of information sheets and booklets for patients and their families.

### **Chest Heart and Stroke Scotland**

Third Floor, Rosebery House, 9 Haymarket Terrace, Edinburgh EH12 5EZ

Phone: 0131 225 6963

Freephone helpline: 0845 0776000

Email: [admin@chss.org.uk](mailto:admin@chss.org.uk)

Website: [www.chss.org.uk](http://www.chss.org.uk)

Chest Heart and Stroke Scotland provides a 24 hour advice line offering confidential, independent advice on all aspects of chest, heart and stroke illness. A series of information booklets, factsheets and videos are available free of charge to patients and carers.

### **Lifeblood: The Thrombosis Charity**

PO Box 58, Llanwrda SA19 0AD

Phone: 01558 650 222

Email: [lifeblood.charity@googlemail.com](mailto:lifeblood.charity@googlemail.com)

Website: [www.thrombosis-charity.org.uk](http://www.thrombosis-charity.org.uk)

Lifeblood's website includes a range of information on various conditions linked with thrombosis.

### **NHS Inform**

Website: [www.nhsinform.co.uk/](http://www.nhsinform.co.uk/)

NHS Inform provides quality-assured health information for the public



[www.healthcareimprovementscotland.org](http://www.healthcareimprovementscotland.org)

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Telephone 0131 623 4300 Fax 0131 623 4299

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The Healthcare Environment Inspectorate, the Scottish Health Council, the Scottish Health Technologies Group, the Scottish Intercollegiate Guidelines Network (SIGN) and the Scottish Medicines Consortium are key components of our organisation.



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