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Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Bulletin
"Independent prescribing information for NHS Wales"

Atrial fibrillation

Atrial fibrillation (AF) is the most common arrhythmia but, even when asymptomatic, it is not benign. The main complication of AF is systemic thromboembolism, usually cerebral. Overall, AF is associated with a fivefold increase in the risk of stroke,[1] and twice the risk of death,[2] predominantly linked to the presence and severity of underlying cardiovascular disease. It can also significantly impact a person's quality of life (e.g. their exercise tolerance and cognitive function). With ageing populations, the prevalence of AF is increasing.

Risk factors for AF include male gender, advanced age, obesity, hypertension, diabetes, coronary artery disease, and left-ventricular dysfunction.[1,2] Other cardiac conditions commonly associated with AF include valvular disease and ischaemia; heart failure (HF) is both a cause and an effect of AF. These comorbidities significantly impact prognosis. Other common causes can be acute (e.g. surgery or alcohol toxicity) or reversible, such as pulmonary or metabolic disease (e.g. hyperthyroidism). In the presence of such conditions the AF is considered "secondary".[2] When, as in many cases, no cause is identified it is termed "lone AF".

Therapy for AF involves the control of heart rhythm and/or rate alongside antithrombotic measures. Despite available treatments, a large number of strokes and deaths remain attributable to sub-optimal management of AF. Inadequate anticoagulation or failure to anticoagulate, particularly in many elderly patients, has been identified as a problem.[3,4]

The National Service Framework for Older People in Wales specifies the need to manage AF effectively as part of a stroke prevention strategy.[5] The Quality and Outcomes Framework of the General Medical Services contract stipulates that general practices have a register of patients with AF. Points are also dependent on the percentage of these patients who have a diagnosis made since 1 April 2008 that has been confirmed with electrocardiogram (ECG) or by a specialist, and those who are receiving anticoagulant or antiplatelet therapy.[6]

Summary

- The initial management of AF for patients who are haemodynamically stable and whose symptoms are tolerable should be aimed at controlling heart rate and preventing thromboembolism.
- Correctable underlying disorders and risks for cardiovascular disease should also be managed.
- Appropriate selection of rate control and antithrombotic medication is discussed. Therapy should be reviewed whenever a patient's risks are re-evaluated.
- Selected patients may be referred for cardioversion and rhythm control. Long-term anti-arrhythmic therapy used for prevention of AF recurrence is discussed on pages 2 - 3.
- Therapy for AF continues to evolve – ongoing research investigates the impact of new surgical procedures and medicines. These are outlined briefly in the relevant sections.

In addition to the diagnosis and management of AF, detection is also identified as an area for possible improvement. The NHS Stroke Improvement Programme is researching various approaches, including both systematic and opportunistic pulse palpation.[4] Because the personal and economic burden of stroke and other complications is so high, effective prevention strategies are not only desirable but usually cost-effective.

Investigating AF in a person with an irregular pulse requires a history, physical examination, and an ECG (ambulatory, if necessary).[1,7] The pattern of AF episodes will determine the classification of disease (see Box 1).[1,2] The different categories of AF are not mutually exclusive, nor do they necessarily correspond to different overall morbidity or mortality rates. They are, however, used to help prioritise treatment options. Further investigations, such as transthoracic or transoesophageal echocardiography may be required to help determine appropriate management in certain patients.[1]

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Box 1. Classification of AF*

Category	Characteristics
First-detected or recent onset	One diagnosed episode (may be an incidental finding)
Paroxysmal	Recurrent self-limiting episodes that terminate in < 7 days
Persistent	Recurrent episodes lasting > 7 days; not self-terminating
Permanent	Long-standing; termination of AF not achieved or not attempted

* Episodes lasting more than 30 seconds and not secondary to other manageable causes.

Management

Haemodynamically **unstable** patients with rapid AF and acute symptoms require urgent assessment in hospital for cardioversion and/or rapid control of heart rate, and anticoagulation.[7] Initial management in primary care, for patients who are **stable** and whose symptoms are tolerable, should be heart rate control and suitable antithrombotic therapy. Cardiovascular risk factors should also be managed.

Prescribers should be mindful that some medicines can cause AF, such as bronchodilators and levothyroxine. They should also be careful to ensure that the management of cardiovascular risk factors is adequate but does not in itself precipitate AF; for example, diuretic-induced hypokalaemia, which can cause AF, is reported in over 8% of patients receiving thiazides in primary care.[8]

Patients who will need to be referred for further specialist assessment are: those in whom further investigations of cardiac function are required and/or in whom categorisation of disease is difficult; those who remain symptomatic despite rate control, or in whom rate control measures fail; and those requiring assessment for rhythm control (including those who present within 48 hours of AF onset).

Rhythm vs rate control

Evidence comparing the two strategies does not favour either with regard to mortality, major cardiovascular events, or stroke.[2,7] The aim of treatment is to improve quality of life for as long as possible by improving symptoms, reducing the risk of long-term sequelae, and limiting the potential adverse effects of medication.[2]

Rhythm control is currently the preferred option for patients with paroxysmal AF, and for those with persistent AF and one of the following: age 65 or below, symptomatic disease, first-time presentation of lone AF, AF secondary to a treated or corrected precipitant, or HF.[1] The evidence supporting this selection of patients is not strong.[1,7] In a recent study of AF in patients with HF, rhythm control provided no advantages over rate control.[9]

There will be some patients (e.g. those over 65 who are symptomatic) for whom either a rate control or a rhythm control strategy would appear to be appropriate.[1] Ultimately the decision to focus on one or the other will depend on the balance of risk and benefits likely to be realised in an individual.

Rate control

Rate control should be started in stable patients presenting with AF. It is the recommended strategy for long-term management of patients with permanent AF, and those with persistent AF who are aged over 65, who have coronary artery disease, who are without HF, who are unsuitable for cardioversion, or who have contraindications to anti-arrhythmics.[1]

Beta-blockers or the rate-limiting calcium channel blockers (CCBs), diltiazem or verapamil, are the preferred options for initial monotherapy.[1] These medicines are considered equally effective in controlling heart rate in AF patients (although diltiazem is not licensed for AF).[1] Because digoxin is ineffective in the presence of significant sympathetic activation, it is only considered an alternative if exercise tolerance is not a concern, i.e. in sedentary patients in whom the other agents are unsuitable.

If heart rate and symptoms are not controlled, the dose may need to be increased or, if maximum doses are being used, digoxin may need to be added. For patients undertaking normal activities, digoxin can be combined with either a beta-blocker or a CCB. If a patient's heart rate needs to be controlled during exercise, digoxin should be combined with a CCB. (In the latter case, a patient already on a beta-blocker may need to have digoxin introduced before they are switched to a CCB.) Beta-blockers and verapamil should not be combined because of the significant risk of bradycardia and reduced cardiac output.

Rhythm control

Cardioversion is attempted only in selected patients. In the majority of patients in whom sinus rhythm is restored, whether spontaneously or after electrical or pharmacological conversion, AF will recur.[10,11] Without long-term anti-arrhythmic medication after cardioversion, 70-80% of patients will be back in AF within a year. It is the potential adverse effects associated with anti-arrhythmic medication that limit the application of a rhythm control strategy.

For maintenance of sinus rhythm, a standard beta-blocker is recommended first-line.[1] Further treatment options include: class Ic anti-arrhythmic agents, such as flecainide or propafenone; sotalol; and amiodarone. Decisions made by specialists regarding the use of these agents depend on a patient's treatment history and the presence of any structural heart disease. Selected patients with paroxysmal AF who have infrequent episodes and few symptoms may be maintained using a "pill-in-the-pocket" approach.[1] These patients self-administer anti-arrhythmic medication, such as flecainide, with the onset of an AF episode.

If a patient is successfully maintained in sinus rhythm for six months they can be discharged from hospital care when an appropriate management plan has been agreed with their general practitioner.[1] It is the inherent toxicity of the most effective anti-arrhythmic for AF prevention, amiodarone, that causes most concern with follow-up in primary care. In Wales, prescribing of amiodarone should only be transferred to primary care under shared care arrangements when a patient is established on a maintenance dose.[12]

Dronedarone is a oral anti-arrhythmic agent that has recently become available. It is a derivative of amiodarone that can slow rate and prevent recurrence of AF in stable patients with non-permanent AF. It appears to be associated with fewer adverse events than amiodarone but it is reported to be less effective. The National Institute for Health and Clinical Excellence (NICE) is currently reviewing its use.[13] Vernakalant is another agent that may become available. It is an ion channel blocker that has been developed as an intravenous product for cardioversion and as oral medicine to prevent recurrence of AF.[14] An application for marketing has been submitted to the European Medicines Evaluation Agency.

Non-pharmacological therapies

A number of catheter and surgical techniques have been developed to complement or replace the use of anti-arrhythmic agents. For older patients with poor heart rate control the "ablate-and-pace" approach may help: catheter ablation destroys the atrioventricular node and a pacemaker provides a regular pulse. The atria continue to fibrillate so anticoagulation is still required. For younger patients with symptomatic AF resistant to medical therapy, catheter ablation to isolate the pulmonary veins may be effective in maintaining sinus rhythm and allow withdrawal of warfarin in the long-term. For patients requiring cardiac surgery who have coexisting AF, surgical ablation of the left atrium may achieve a similar result.[2,7]

Antithrombotic therapy

All patients with AF, irrespective of the classification of disease, should receive antithrombotic therapy.[1] Patients undergoing cardioversion need to receive an anticoagulant. Heparin is used in the acute setting and when AF has an onset of less than 48 hours. Otherwise, warfarin should be used for three weeks before and for at least four weeks after cardioversion.

For long-term antithrombotic protection in patients with non-valvular AF, the choice between using an anticoagulant (warfarin) or an antiplatelet (aspirin) depends on an individual assessment of risk for both stroke and bleeding. Warfarin is the more effective agent: it reduces the rate of stroke by 64% compared to a reduction of 22% with aspirin.[15] The greatest reduction is observed in those patients at highest risk, such as those who have had a previous stroke or transient ischaemic attack (TIA) – these patients have a stroke risk of approximately 12% annually if untreated.[2,15] To broadly quantify the effect of therapy, aspirin reduces this risk to about 10%, whereas warfarin reduces it to about 5%.

Although the rate of serious bleeding events associated with warfarin is twice that of aspirin, the increase in absolute risk is small (0.2% per year).[15] Thus, the potential benefit of warfarin therapy (target INR 2.5) is clear in high-risk patients (see Box 2).[1] In patients who have a low risk of stroke (approximately 1-2% annually), the benefits of warfarin therapy do not outweigh the risks and aspirin can be recommended.[1,2] The threshold for anticoagulation in patients with a moderate level of risk is less straightforward. These patients may be considered for either warfarin or aspirin therapy.[1]

Box 2. NICE Classification of stroke risk[1]

Category of risk	Risk factors
High	Previous ischaemic stroke/TIA or thromboembolic event. Age ≥ 75 with hypertension, diabetes, or vascular disease. Evidence of valve disease, HF, or impaired left-ventricular function on echocardiography.*
Moderate	Age ≥ 65 with no high risk factors. Age < 75 with hypertension, diabetes, or vascular disease.
Low	Age < 65 with no moderate or high risk factors.

* Not a routine investigation to establish stroke risk but can be used to refine risk stratification.

It must be appreciated that the risk of stroke is a composite of interacting risks. Having two or more "moderate" thromboembolic risk factors (e.g. hypertension and diabetes) may put a patient at higher risk than having only one (e.g. age over 65). If this is the case, the patient may favour warfarin over aspirin.

To help predict the risk of stroke and aid decisions regarding the most appropriate thromboprophylaxis, several scoring systems have been developed. These are based on different clinical trial cohorts to that used by NICE but produce broadly comparable results. The $CHADS_2$ risk tool (see Box 3) predicts higher rates of stroke in patients with higher scores.[2]

Box 3. $CHADS_2$ scoring system

	Risk factor	Score
C	Congestive HF/left-ventricular dysfunction	1
H	Hypertension	1
A	Age > 75	1
D	Diabetes	1
S	Stroke/TIA/thromboembolism	2

Refinements to these risk stratification schemes continue to be sought. One revised scoring system that is based on modified criteria (CHA_2DS_2-VASc, see Box 4) has shown some improvement in predictive value.[16] This system predicts low event rates in low-risk patients (score 0), but categorises fewer patients with intermediate risk (a score of 1) and more patients with high risk (a score ≥ 2).

Box 4. CHA_2DS_2-VASc scoring system

	Risk factor	Score
C	Congestive HF/left-ventricular dysfunction	1
H	Hypertension	1
A	Age ≥ 75	2
D	Diabetes	1
S	Stroke/TIA/thromboembolism	2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
A	Age 65 - 74	1
Sc	Sex category, i.e. female gender	1

When deciding whether long-term warfarin therapy is appropriate, the risk of stroke must be balanced against the risk of bleeding. Communicating these risks can be difficult and using visual aids to help patients understand numerical information can be useful.[17] A set of patient decision aids for atrial fibrillation are available at: www.npci.org.uk/therapeutics/cardio/atrial/resources/pda_af.pdf.

When assessing bleeding risk, particular care is needed in patients with the following risk factors:

- age over 75.
- concomitant use of antiplatelet agents or nonsteroidal anti-inflammatory drugs.
- use of multiple other medicines (the use of antibiotics and herbal products can be problematic).
- uncontrolled hypertension.
- a history of bleeding (e.g. peptic ulcer or cerebral haemorrhage), or anaemia.
- a history of poorly controlled anticoagulation therapy, or INR > 3.
- bleeding tendencies (due to coagulation defects).
- hepatic or renal insufficiency.
- malignancy.
- alcohol abuse.
- cognitive impairment.
- an excessive risk of trips and falls.[1,18,19]

Further specific risk factors have been incorporated into one scoring system that has been used in outpatients to estimate the risk of major bleeding related to warfarin.[7,20] In addition to advanced age and a history of stroke or of bleeding, the presence of diabetes, recent myocardial infarction, a packed cell volume below 30%, or a creatinine above 1.5 mg/dL [130 µmol/L] are taken into account.[20]

While the risk of bleeding must be considered in any patient on antithrombotic therapy, it is important that appropriate therapy is initiated and that a decision to anticoagulate a patient is not compromised by inadequate management. Many patients, especially elderly patients, are undertreated.[3] Evidence confirms that despite a higher risk of haemorrhage, the elderly are among those that obtain benefit from warfarin therapy.[21] Monitoring elderly patients more closely and lowering the INR target to 2 in patients over 75 years may be considered.[2]

It should be noted that alternative antithrombotic therapy cannot be routinely recommended.

- Combining warfarin with an antiplatelet agent is associated with greater risk of bleeding.[1] Combined therapy may be initiated in secondary and tertiary settings in selected patients with significant comorbidity (e.g. stents or prosthetic valves).
- The combination of aspirin and clopidogrel is not as effective as warfarin.[22] In patients considered unsuitable for warfarin, the combination has been shown to be more effective than aspirin alone, but it is associated with higher risk of bleeding.[23,24]
- Clopidogrel alone is not a substitute for aspirin – there is no evidence to support its use in AF.

Dabigatran, a direct thrombin inhibitor, is being investigated as an alternative to warfarin for stroke prevention in AF patients. Dabigatran has a rapid onset of action and does not require therapeutic monitoring. In a large randomised trial, 110 mg of dabigatran had a similar effect on stroke and a lower risk of major haemorrhage compared with warfarin; a 150 mg dose had an improved effect on stroke with a similar risk of haemorrhagic events.[25]

The Summaries of Product Characteristics should be consulted for full prescribing information.

References

1. The National Collaborating Centre for Chronic Conditions for the National Institute for Health and Clinical Excellence. Atrial Fibrillation. NICE clinical guideline 36. June 2006. http://guidance.nice.org.uk/CG36/Guidance/pdf/English
2. Fuster V et al. ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation – Executive summary. Circulation 2006; 114: 700-752. http://circ.ahajournals.org/cgi/content/full/114/7/700
3. Gladstone DJ et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. Stroke 2009; 40: 235-240.
4. NHS Stroke Improvement Programme. Atrial fibrillation-detection and optimal therapy in primary care. November 2009. www.evidence.nhs.uk/qualityandproductivity
5. Welsh Assembly Government. National Service Framework for Older People in Wales. March 2006.
6. BMA and NHS Employers. Quality and Outcomes Framework guidance for GMS contract 2009/10. March 2009.
7. Lafuente-Lafuente C et al. Management of atrial fibrillation. BMJ 2009; 339: b5216. doi: 10.1136/bmj.b5216.
8. Clayton JA et al. Thiazide diuretic prescription and electrolyte abnormalities in primary care. Br J Clin Pharmacol 2005; 61: 87-95.
9. Roy D et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008; 358: 2667-2677.
10. Schilling R. Cardioversion of atrial fibrillation and the use of antiarrhythmic drugs. Heart 2009. doi: 10.1136/hrt.2008.155812.
11. Lafuente-Lafuente C et al. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation (review). Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005049. DOI: 10.1002/14651858.CD005049.pub2.
12. All Wales Medicines Strategy Group. Shared care template – Amiodarone. June 2008. www.awmsg.wales.nhs.uk
13. NICE. Atrial fibrillation – dronedarone: appraisal consultation document. December 2009. www.nice.org.uk/guidance
14. www.nelm.nhs.uk/en/NeLM-Area/News/2009---August/27
15. Hart RG et al. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007; 146: 857-867.
16. Lip GYH et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on Atrial Fibrillation. Chest 2010; 137: 263-272.
17. Helping patients understand risks – 7 simple strategies. WeMeReC Bulletin. September 2006.
18. Gage BF et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J 2006; 151: 713-719.
19. Monitoring anticoagulant therapy in primary care. WeMeReC Bulletin. March 2007. www.wemerec.org.uk
20. Aspinall SL et al. Bleeding Risk Index in an anticoagulant clinic. J Gen Intern Med 2005; 20: 1008-1013.
21. Mant J et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007; 370: 493-503.
22. The ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised control trial. Lancet 2006; 367: 1903-1912.
23. The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009; 360: 2066-2078.
24. Verheugt FWA. Who is ineligible for warfarin in atrial fibrillation? Lancet 2009; 374: 510-511.
25. Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. [RE-LY] N Engl J Med 2009; 360: 1139-1151.

Notes

Actions

1. *Identify patients on amiodarone…*

2. *Look at patient communication aids…*

3.