Management of atrial fibrillation: an overview of the NICE guidance on AF management

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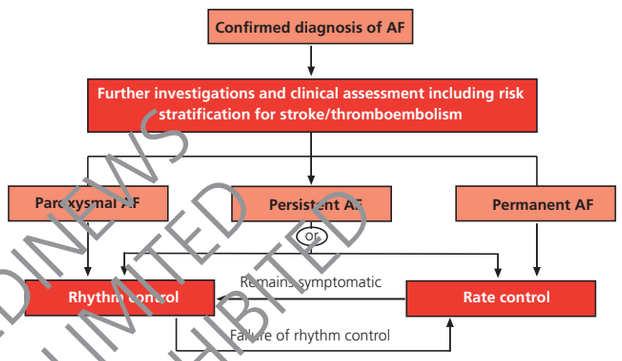
Abstract

This article aims to provide an overview of the management of atrial fibrillation (AF), with reference to the recently published National Institute for Health and Clinical Excellence (NICE) guidelines on AF management (http://www.nice.org.uk/CG36/guidance/pdf/english). This article is not meant to cover the whole guideline nor be a systematic review, as the full guideline contains all the search strategies and appraised evidence tables, and represents a comprehensive assessment of the evidence behind the recommendations in the NICE guideline (also available at http://rcplondon.ac.uk/pubs/books/af/index.asp).

Key words: atrial fibrillation, NICE, guidelines.

Br J Cardiol 2007;**14**:23–8

Figure 1. Treatment strategy decision tree



Key: AF = atrial fibrillation

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Introduction

The management of atrial fibrillation (AF) has, for many years, varied significantly between physicians, with often much debate as to the optimal approach to be taken.[1] Since AF is associated with a substantial excess of both morbidity and mortality, it is clear that a streamlined guideline-based approach to management is necessary.[2]

Notably, AF and its complications now consume 1% of the UK National Health Service budget.[3] Hence, the recent publication of evidence-based guidelines from the National Institute for Health and Clinical Excellence (NICE) could not be more appropriate.[4] Other guidelines are also available, such as the joint American College of Cardiology/American Heart Association/European Society of Cardiology guidelines (recently updated in 2006) and the American College of Chest Physicians guidelines on antithrombotic therapy for AF.[5,6] Some aspects of these guidelines merit comment.

Most guidelines on AF management are largely 'expert consensus-based' i.e. formulated by a large group of cardiology experts following a review of the published evidence. The NICE guidelines on AF management are different as the methodology was based on systematic reviews of the world literature performed (by an information specialist) following definition of the guideline scope.[4] The scope itself underwent public consultation and was modified in line with suggestions from stakeholders to address key areas pertaining to AF management that are applicable to UK clinical practice. These systematic reviews were then critically appraised (by a health services researcher) and cost-effectiveness analyses applied (by a health economist). The distilled, appraised evidence thus gathered was then debated by a multi-disciplinary Guideline Development Group (GDG), which consisted of cardiologists (only three), general physicians, nurses, pharmacists, general practitioners and two lay representatives (one of whom had AF). The recommendations were then formulated. The GDG was led by a Chair (a physician who was a non-cardiologist) and a Clinical Adviser (a cardiologist with special interest in AF management). Invited experts, including a stroke physician, cardiac surgeon and a haematologist, also contributed where evidence for some sections were being debated.

The draft NICE guideline then underwent two rounds of public stakeholder consultation, which was followed by the formal publication of the guideline in June 2006. The remit of the NICE guideline on AF management was to be practical and pragmat-

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ic which would be applicable for more than 80% of AF patients for over 80% of the time in the UK setting.

Classification

AF is now generally classified according to the temporal pattern of presentation as: i) recent onset (within 48 hours); ii) paroxysmal; iii) persistent (duration seven days or more); or iv) permanent (duration greater than one year or refractory to cardioversion attempts).[4,5,7] This simple classification (see figure 1) merely offers an idea of the likely time course of AF and may help guide management objectives.

In reality, management of patients with AF should be guided by many considerations, including symptoms, haemodynamic stability and associated co-morbidities (such as hypertension and heart failure).

Symptoms

Patients with AF can present with a wide variety of symptoms and many are asymptomatic. Where AF is suspected, it is important to confirm the diagnosis before initiating management strategies. Patients presenting with any of the following: breathlessness/dyspnoea, palpitations, syncope/dizziness, chest discomfort, and stroke/transient ischaemic attack etc, should have manual pulse palpation performed to assess for the presence of an irregular pulse that may indicate underlying AF. This should then be confirmed electrocardiographically.[4]

Investigation of AF

The assessment of the patient with AF needs to be methodical. As always, a thorough history taking and clinical examination are essential and may alert the physician to potential causes for AF and the impact on the patient's lifestyle.

To confirm the diagnosis of AF, an electrocardiogram (ECG) should be performed in all patients in whom AF is suspected because an irregular pulse has been detected, whether symptomatic or not. A blood workup (full blood count, electrolytes and thyroid function tests) and chest X-ray are essential; an echocardiogram is often useful.

In patients with suspected paroxysmal AF, which is undetected by standard ECG recording, the NICE guidelines suggest that a 24-hour ambulatory ECG monitor should be used in those with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart. However, a seven-day Holter or an event recorder ECG should be used in those with symptomatic episodes more than 24 hours apart.

Rate control or rhythm control

Theoretically, restoration of sinus rhythm should offer the premise of improved haemodynamics and symptom relief, whilst potentially reducing the thromboembolic tendency and stroke risk. Unfortunately, this is often unrealistic. The tendency in many patients with AF is towards recurrence (often asymptomatic) even if rhythm control succeeds initially. Even when using an aggressive serial cardioversion strategy for relapse, approximately half the patients remain in sinus rhythm at one year.[8] At five years, only 25% remain free of AF.[9] These recurrences may be asymptomatic and thereby still confer an increased risk of stroke, of which the clinician may be unaware. This knowledge means that many patients should be considered for long-term anticoagulation even if rhythm control has apparently succeeded.[10]

As to whether rhythm or rate control should be offered as first line, some data from clinical trials are available. Large studies such as the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial[11] suggest that rate control is not an inferior strategy to rhythm control. There was no difference in the primary end point of overall mortality at five years and no significant difference in the composite secondary outcome measure of death, disabling stroke, disabling anoxic encephalopathy, major bleeding and cardiac arrest, between the study arms.

Importantly, a rhythm control strategy was associated with a higher rate of hospitalisations and more frequent adverse drug reactions. An interesting post-hoc analysis of the predictors of survival in the AFFIRM study showed that anticoagulation therapy and sinus rhythm were potent predictors of survival. However, a greater mortality associated with anti-arrhythmic drug use offset the survival advantage of maintaining sinus rhythm.[12] This implies that survival would be improved if better drugs or techniques to maintain sinus rhythm were available.

Of course, extrapolating such clinical trial data to the 'real world' can be fraught with difficulties. To help guide clinical decisions, the NICE guidelines have suggested that rhythm control should be offered to the following patients as the preferred initial option: those with lone AF, or AF secondary to a corrected precipitant (e.g. alcohol); patients with symptoms despite optimal rate control; and patients with heart failure. However, these categories are not mutually exclusive from those where a rate control strategy is the preferred option. Thus, associated co-morbidities and patient choice should be considered.

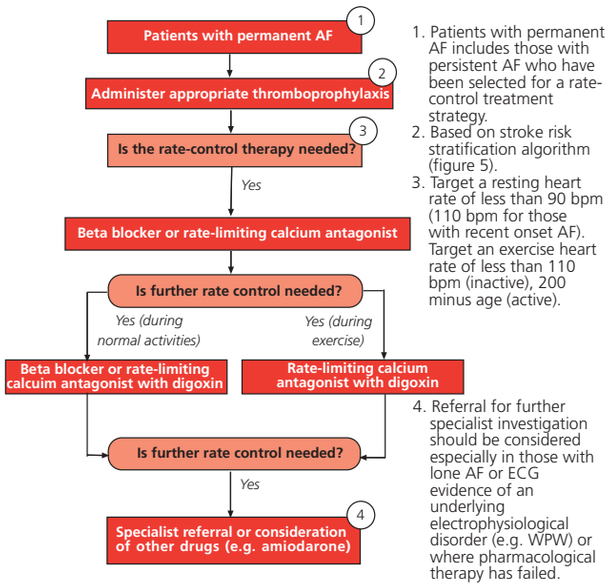
Drug therapy for atrial fibrillation

The crux of management of acute AF is primarily an assessment of haemodynamic stability. In those with life-threatening features (haemodynamic compromise, severe cardiac decompensation, angina etc), emergency electrical cardioversion should always be considered irrespective of duration of onset.[4,13] In the more stable patient, a rate-limiting calcium channel blocker or beta blocker should be tried as first line, but where these are inappropriate (e.g. pulmonary oedema), intravenous amiodarone is preferred.

It is also important to consider electrophysiological abnormalities, such as Wolff-Parkinson-White syndrome, as an underlying diagnosis, particularly in younger patients without evidence of structural or ischaemic heart disease. In this situation, atrioventricular node-blocking agents (e.g. diltiazem, verapamil, or digoxin) should not be used as these may exacerbate the ventricular rate and are potentially dangerous. Here it would be appropriate to consider intravenous flecainide for attempting pharmacological cardioversion.[4,14]

It is generally accepted that a resting heart rate below 90 bpm is optimal whilst, on exertion, the heart rate should not

Figure 2. Rate-control treatment algorithm for permanent (and some cases of persistent) atrial fibrillation



Key: AF = atrial fibrillation; bpm = beats per minute; ECG = electrocardiogram; WPW = Wolff-Parkinson-White

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exceed 110 bpm in the sedentary patient or '200 minus age' in the ambulatory patient.[4,15] For many years, the mainstay of drug therapy for rate control in AF was the cardiac glycoside, digoxin. This drug is of limited efficacy, however, in the context of hyperadrenergic states, namely thyrotoxicosis, fever, peri-operatively and – most importantly – during exercise.[16,17] Thus, digoxin monotherapy is only likely to offer adequate rate control in elderly sedentary patients.[4] The algorithm for rate control for permanent AF from the NICE guideline is illustrated in figure 2.

Beta blockers are particularly effective at controlling ventricular rate and should be used as first-line agents. Additionally, beta blockade also reduces the chance of recurrence following successful cardioversion, and these drugs are useful first-line agents in paroxysmal AF. In the peri-operative setting, beta blockers reduce the likelihood of developing AF in those deemed at risk.

The rate-limiting, non-dihydropyridine calcium channel blockers (diltiazem, verapamil) are also frequently used to optimise rate control in those unable to take or tolerate a beta blocker. Although digoxin is no longer considered first line, it remains a useful adjunct in patients who remain tachycardic at rest and can be used in combination with either beta blockers and calcium channel blockers as combination therapy.[4,15] Despite these drugs, some will continue to have poor control of ventricular rate. In these circumstances, agents such as amiodarone are advised. This drug is also useful in those with paroxysmal AF and frequent relapses (despite adequate doses of first-line anti-arrhythmic agents, such as class 1c drugs (e.g. flecainide, propafenone and sotalol). Sadly, the potent nature of amiodarone means side effects are common, particularly with prolonged exposure.[18] This drug is, therefore, usually initiated only under specialist guidance so that patients can be followed-up in the long-term.

Cardioversion

In persistent AF, cardioversion can be performed electrically or pharmacologically. Electrical cardioversion may be initially successful in 75–93% of patients but this depends strongly on the duration of AF (success rates are particularly poor after one year), left atrial size and co-existing structural heart disease.[4,19-21] Pharmacological cardioversion can be achieved using a number of drugs but, in the UK, the most commonly used agents are flecainide and amiodarone. There is often little to choose (apart from speed of action) between oral and intravenous administration, with successful cardioversion reported in up to 80% with oral flecainide therapy, rising to 90% with intravenous administration.[4] As relapse following cardioversion is common, anti-arrhythmic drugs are often required to improve the likelihood of long-term maintenance of sinus rhythm. Beta blockers are the most commonly used drugs for this purpose, although long-term amiodarone is required in some patients (particularly those who are heavily symptomatic with AF), whilst flecainide and other class I drugs are used in younger patients without structural or ischaemic heart disease.[4]

Side effects

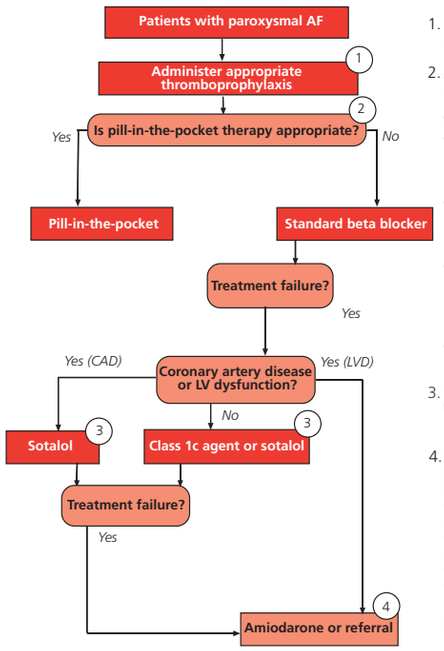
All anti-arrhythmic drugs have side effects but the problem is particularly pertinent with class I and III drugs. These alter the fluctuation of potassium or sodium channels of atrial cells and can thereby modify the refractory period, resulting in QT and QRS prolongation.[22] This can potentially lead to the life-threatening arrhythmias, including 'torsades de pointes', in up to 5% of patients.[22,23] Several factors have been identified as conferring increased risk for this, including the following: hypokalaemia or hypomagnesaemia, congenitally prolonged QT intervals, bradycardia, congestive heart failure, female sex, pauses associated with the conversion of AF to sinus rhythm, and concomitant use of medications, especially those which interfere with the hepatic metabolism of anti-arrhythmic drugs, such as erythromycin.[23]

It is therefore advisable that caution be used in prescribing these drugs and a 12-lead ECG sought after treatment initiation, to assess for QT prolongation. Additionally, some class Ic drugs can convert AF into atrial flutter with 1:1 atrioventricular nodal conduction, with resultant haemodynamic instability. Thus, concomitant use of atrioventricular nodal blocking agents, such as beta blockers or rate-reducing calcium channel blockers, is usually recommended.

Treatment algorithms

The algorithms from the NICE guideline for the management of

Figure 3. Rhythm control treatment algorithm for paroxysmal atrial fibrillation



1. Based on stroke risk stratification algorithm (figure 5)
2. A pill-in-the-pocket strategy should be considered in those who:
   - have no history of left ventricular dysfunction, or valvular or ischaemic heart disease
   - have a history of infrequent symptomatic episodes of paroxysmal AF
   - have a systolic blood pressure greater than 100 mmHg and a resting heart rate above 70 bpm,
   - are able to understand how to and when to, take the medication.
3. Sotalol to be progressively titrated from 80 mg twice daily up to 240 mg twice daily.
4. Referral for further specialist investigation should be considered, especially in those with lone AF or ECG evidence of an underlying electrophysiological disorder (e.g. WPW) or where pharmacological therapy has failed.

Key: AF = atrial fibrillation; LV = left ventricular; ECG = electrocardiogram; WPW = Wolff-Parkinson-White

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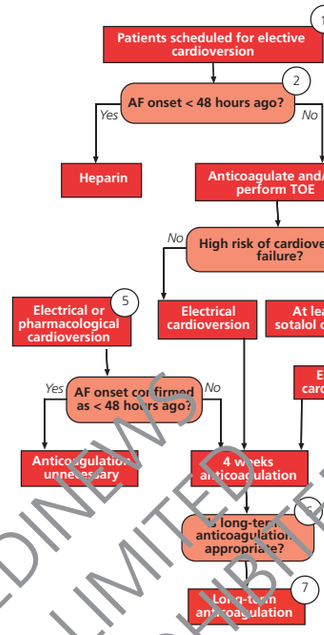
Figure 4. Cardioversion treatment algorithm



1. Perform TTE examination prior to rhythm-control treatment strategy involving cardioversion.
2. Also consider patient preferences following a discussion of the advantages and disadvantages of each option.
3. Administer at least 3 weeks therapeutic anticoagulation prior to cardioversion or perform TOE-guided cardioversion depending on preference contraindications and practicalities.
4. High risk of cardioversion failure suggested by previous failure of AF recurrence.
5. Intravenous amiodarone as drug of choice in those with structural heart disease, flecainide in those without structural heart disease.
6. As determined by the stroke stratification algorithm or where there is a high risk of AF recurrence. Patients with a history of AF > 12 months, mitral valve disease, LV dysfunction, enlarged left atrium and a history of AF recurrence are at a higher risk of AF recurrence.
7. Anticoagulation should be administered to a target INR of 2.5 (range 2.0 to 3.0)

Key: AF = atrial fibrillation; TTE = transthoracic echocardiography; TOE = transoesophageal echocardiography; LV = left ventricular

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patients with paroxysmal AF and cardioversion for those with persistent AF are shown in figures 3 and 4, respectively.

Non-pharmacological treatments

For those who continue to be symptomatic or where anti-arrhythmic drugs are ineffective or intolerant, non-pharmacological approaches can be considered. A variety of catheter-based approaches (such as pulmonary vein isolation and atrioventricular nodal modification) and surgical procedures (e.g. Maze) are available as potential treatments for AF. A full discussion of this topic is beyond the scope of this brief overview.

The NICE guidelines suggest that referral for such further specialist interventions should be considered in the following: those in whom pharmacological therapy has failed; those with lone AF; and those with ECG evidence of an underlying electrophysiological disorder (e.g. Wolff-Parkinson-White syndrome). The reasons for referral for specialist intervention should be explained and discussed with the patient.

Antithrombotic therapy

Much of the morbidity and mortality associated with AF is related to the significant associated risk of stroke and thromboembolism. AF increases the risk of stroke by up to five-fold across all age groups and accounts for up to 15% of all ischaemic stroke.[24] With age, the association continues to strengthen and in those over 80 years, AF accounts for nearly 25% of strokes, especially in the presence of co-morbidities.[24] Of particular alarm is that those with AF, who have a stroke, have a poor outcome with greater disability, mortality and longer hospital stays.[25]

A recent meta-analysis of 13 randomised trials demonstrated that, compared to placebo, adjusted-dose warfarin offers a reduction in risk of ischaemic stroke or systemic embolism by two-thirds.[26] This effect was greater for secondary compared to primary stroke prevention. Importantly, the efficacy of warfarin is only conferred by adequate anticoagulation and a target INR of 2.0–2.5 should be maintained in most patients, as the risk of stroke increases two-fold in those with an INR 1.5–2.0, and higher still in those with an INR < 1.5.[27]

A meta-analysis of the six main randomised, controlled trials of aspirin versus placebo demonstrated that aspirin treatment offers a significant stroke risk reduction of 22% (95% CI: 2–38).[28] This rather unimpressive figure is broadly similar to the effect seen in vascular disease patients and may therefore simply reflect the effect of aspirin on the various vascular risk factors

(e.g. diabetes and hypertension) that commonly co-exist with AF. Additionally, stroke in aspirin-treated AF patients is frequently more severe, often with greater mortality and disability. Aspirin should therefore be considered an inferior substitute for warfarin in high-risk AF patients.

Despite convincing evidence in favour of warfarin, many physicians continue to avoid appropriate anticoagulation prescription.[29-33] This pattern is most commonly seen in the elderly and those with a history of falls or bleeding events. Although safe prescribing must always be practised, these patients often do represent those at highest risk of stroke and, wherever possible, a full discussion and assessment of bleeding risk should be made. Additionally, up to 40% of patients would prefer not to receive warfarin[34] and may press the physician towards the prescription of aspirin instead.

The potential pitfalls of this must be discussed with each patient and should be balanced with the knowledge that many patients perceive a moderate-to-severe stroke as worse than death.[35] Additionally, anticoagulation decisions should not be unduly delayed as there would appear to be a clustering of thromboembolic events around the time of AF onset.

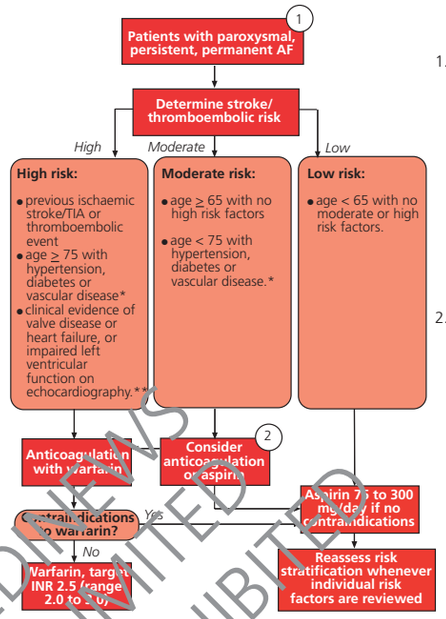
Numerous risk stratification protocols have been proposed[4,36] in an effort to identify high-risk patients with AF who should be targeted for anticoagulation. One popular and well-validated risk stratification scheme is $CHADS_2$ where one point is given for: Congestive heart failure, Hypertension, Age ≥ 75 years and Diabetes mellitus, and two points for Stroke or transient ischaemic attack.[4,36] This scheme highlights the cumulative nature of stroke risk factors, and those with a $CHADS_2$ score of > 2 are 'high risk', whilst those with a score of 0 are low risk.[4,36] The NICE guidelines have opted for an algorithm-based scheme based on modification of the original AF investigators' algorithm[37] and applied in a primary care setting in the United Kingdom (figure 5). The NICE clinical risk stratification defines subjects into low-, moderate- and high-risk categories, this clinical risk stratification scheme has been validated to be broadly similar to the $CHADS_2$ scheme for predicting stroke and vascular event rates.[38]

The assessment of bleeding risk is part of the clinical assessment of AF patients prior to starting anticoagulation therapy, with particular attention being paid to some 'high risk' categories of patients, such as the elderly, those with concomitant use of antiplatelet drugs (aspirin, clopidogrel) or non-steroidal anti-inflammatory agents, those with polypharmacy, uncontrolled hypertension, or a history of bleeding (e.g. peptic ulcer, cerebral haemorrhage) and poorly controlled anticoagulation therapy.[4]

Conclusion

AF represents a growing health epidemic in many ageing Western populations and there is growing emphasis on appropriate management of this condition. Aside from appropriate rate or rhythm control, it is essential for a full and methodical assessment of the individual thromboembolic risk to be carried out. Recent guidelines developed by NICE offer the premise of a streamlined, logical approach to the practical and pragmatic management of AF based on a UK-applicable evidence-based clinical guideline.

Figure 5. Stroke risk stratification scheme algorithm



1. Note that risk factors are not mutually exclusive, and are additive to each other in producing a composite risk. Since the incidence of stroke and thromboembolic events in patients with thyrotoxicosis appears similar to other aetiologies of AF, antithrombotic treatments should be chosen based on the presence of validated stroke risk factors.
2. Owing to lack of sufficient clear-cut evidence, treatment may be decided on an individual basis, and the physician must balance the risk and benefits of warfarin versus aspirin. As stroke risk factors are cumulative, warfarin may, for example, be used in the presence of two or more moderate stroke risk factors. Referral and echocardiography may help in cases of uncertainty.

Key: AF = atrial fibrillation; TIA = transient ischaemic stroke; * = coronary artery disease or peripheral artery disease; ** = an echocardiogram is not needed for routine assessment but refines clinical risk stratification in the case of moderate or severe left ventricular dysfunction and valve disease

Conflict of interest

GL has received funding for research, educational symposia, consultancy and lecturing from different manufacturers of drugs used for the treatment of atrial fibrillation and thrombosis. He is Clinical Adviser to the Guideline Development Group writing the United Kingdom National Institute for Health and Clinical Excellence (NICE) Guidelines on atrial fibrillation management (www.nice.org.uk). TW and ES: none declared.

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