PAPER

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Atrial fibrillation

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ABSTRACT Atrial fibrillation is the most common cardiac arrhythmia in everyday clinical practice, and has a significant morbidity and mortality related to it, either directly or indirectly. Atrial fibrillation results in a heavy burden on NHS services, in terms of both in-patient admissions, and out-patient care. Atrial fibrillation can be symptomatic or asymptomatic, yet morbidity and mortality are not much different in relation to symptom status. However, young patients with 'lone AF' (i.e. AF without 'overt' structural heart disease, as defined by essentially normal clinical history and examination, electrocardiogram, chest X-ray, and, in more recent series, the ECG) are often considered as being 'at low risk', although recent data have been less conclusive on this aspect.

KEYWORDS Atrial fibrilation, management, rate control, rhythm control, stroke prevention, warfarin

LIST OF ABBREVIATIONS Acute coronary syndrome (ACS), Atrial Fibrillation Clopidogrel trial with Irbesartan for prevention of Vascular Events (ACTIVE), atrial fibrillation (AF), cerebrovascular accident (CVA), confidence interval (CI), direct current (DC), electrocardiogram (ECG), international normalised ratio (INR), ischaemic heart disease (IHD), New York Heart Association (NYHA), number needed to treat (NNT), pulmonary vein isolation (PVI), relative risk (RR), relative risk reduction (RRR), renin–angiotensin–aldosterone system (RAAS), transient ischaemic attack (TIA)

DECLARATION OF INTERESTS GYH Lip has a current non-personal interest with Astra-Zenica, Bayer.

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EPIDEMIOLOGY

The incidence and prevalence of AF steeply rises with advancing age. Incidence of AF varies between 0·4 and 0·7 per 1,000 person years at age 50 years, increasing to 1–2% at the age of 80 years; the prevalence of AF ranges from 1·1 per 1,000 patients at 40 years to 105 at 90 years of age. Of note, 70% of AF patients are aged between 65 and 85 years, and overall 84% are older than 65 years.

Table 1 summarises the common risk factors for the development of AF. In general, AF very commonly co-exists with common cardiovascular conditions (such as hypertension, coronary artery disease, heart failure, diabetes, etc.) and males are more affected than females. Increasing age also increases the risk of developing AF, but associated co-morbidities are more frequently seen that can contribute to the complications associated with AF.

Obesity is also increasingly recognised as playing a role in increasing the risk of AF. In the Danish Diet, Cancer and Health Study, for example, the adjusted hazard ratio for AF or atrial flutter per unit of increase in the body mass index was 1·08 (95% CI: 1·05 to 1·11) in men and 1·06 (95% CI: 1·03 to 1·09) in women, whilst the adjusted hazard ratio by obesity was 2·35 (95% CI: 1·70 to 3·25) in men and 1·99 (95% CI: 1·31 to 3·02) in women.

Of the non-cardiovascular causes of AF, heavy alcohol consumption is one of the most common reasons (especially amongst new-onset AF in younger subjects), although AF can be associated with any pyrexial illess, chest infections, thoracic pathology, thyroid disease, post-operative states, etc. Alcohol increases the risk of AF in people drinking more than 42 units per week, and binge drinking ('Saturday night syndrome') is problematic. A more recent associate of AF in young subjects is illicit recreational drug use (cannabis, amphetamines, cocaine, etc.) which essentially precipitates adrenergic-related paroxysms of AF.

CLINICAL CLASSIFICATION

Atrial fibrillation has been classified clinically on the basis of presentation, and such clinical sub-types (although slightly artificial) may help the approach to management as it defines the objective of therapeutic intervention (see Table 2).

Recent onset AF occurs when first diagnosed and seen within 48 hours of presentation, and the objectives here are the assessment of haemodynamic stability (or instability), management of complications (e.g. pulmonary

Risk factor
Age (especially those aged >75)
Male sex
Excess alcohol consumption
Hyperthyroidism
Chronic respiratory diseases
Diabetes
Cardiovascular diseases
Ischaemic heart disease
Valvular heart diseases
Heart failure
Hypertension
Cardiomyopathies
Congenital heart diseases with pre-excitation
Intracardiac masses and tumours
Cor pulmonale
Pulmonary embolism
Pericardial disease
Cerebrovascular disease
Peripheral vascular disease
Recent cardiac and non-cardiac surgery

TABLE 1 Risk factors for development of AF.

oedema), and determination of an initial rate or rhythm control strategy.

More recurrent forms of AF can be paroxysmal or persistent AF. Paroxysmal AF occurs when it is recurrent, intermittent, and self-terminating, and the objective of management here is the reduction of paroxysms and prolonged maintenance of sinus rhythm. Thus, pharmacological or non-pharmacological approaches are used. Persistent AF occurs when AF is recurrent and can be converted to sinus rhythm ('cardioversion') by either pharmacological or electrical interventions.

Where cardioversion is deemed inappropriate or unsuccessful, patients are classed as permanent AF, where the objective of management is rate control. In all clinical subtypes of AF, appropriate antithrombotic therapy should be used, to minimise the risk of stroke and thromboembolism.

ASSESSMENT OF THE PATIENT WITH AF

The key points in the assessment of a patient with AF are summarised in Table 3. Clinical examination is important and basic investigations, including a 12-lead ECG (to document the arrhythmia), chest X-ray, and blood tests (including thyroid status) are mandatory. Most cardiologists would perform a baseline ECG to exclude structural heart disease, although this is not mandatory to decide on thromboprophylaxis, as clinical criteria often suffice. Holter monitoring or cardiomemos (or transtelephonic monitoring devices) are useful in confirming the diagnosis of paroxysmal AF.

Terminology/ classification	Clinical features	Pattern
Initial event (first detected episode)	Symptomatic Asymptomatic (first detected) Onset unknown	May or may not recur
Paroxysmal	Spontaneous termination <7 days Most cases <48 hours	Recurrent
Persistent	Not self-terminating, lasting >7 days or prior cardioversion	Recurrent
Permanent (Accepted)	Not terminated Terminated but relapsed No cardioversion attempt	Established

TABLE 2 Classification of AF.

MANAGEMENT OF AF

The management of AF depends on clinical subtype presentation and symptom severity. As mentioned above, the clinical subtype of AF defines the objective of management, which can be broadly described as 'rhythm control' or 'rate control'.

Comparison of these two management strategies has been informed by recent clinical trials and the merits (or otherwise) have been strongly debated, as summarised in recent reviews.[1–5] In these trials, a large proportion of patients in the 'rhythm control' arms did not maintain rhythm control but were continued in that arm of the trial for the 'intention to treat' analysis. Any treatment strategy should be aimed not only at treating AF, but also at treatment or management of the underlying co-morbidities (especially hypertension), correctable precipitants (e.g. thyroid disease), structural heart disease, or pulmonary disease.

Acute AF

When approaching the patient with acute AF, who may include some patients with recent onset AF who are presenting for the first time, a decision on rate or rhythm control is determined by haemodynamic stability, as well as associated complications (e.g. pulmonary oedema), if present. In patients with a life-threatening deterioration in haemodynamic stability secondary to AF, emergency electrical cardioversion should be performed, irrespective of the duration of its onset.

Some patients with acute AF and a rapid ventricular response develop some haemodynamic instability primarily due to the fast heart rate (underlying heart disease is often present), and an initial attempt at rate control may be appropriate, pending more detailed assessment and investigation. These patients may include

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those with recent onset AF, as well as those with paroxysmal AF who present with a fast paroxysm AF or those with previously stable permanent AF who have developed fast AF. For initial rate control, either a rate-limiting calcium antagonist or beta-blocker (e.g. intravenous esmolol, a short-acting agent) can be tried, but where these are inappropriate (e.g. pulmonary oedema), intravenous amiodarone is preferred.

Other patients may develop haemodynamic instability due to the fact that they have developed fast AF *per se*, and thus, rhythm control with cardioversion is appropriate. Such patients are managed with DC cardioversion, but pharmacological cardioversion with intravenous amiodarone (especially in the setting of underlying left ventricular impairment) is an alternative. In those with known Wolff–Parkinson–White syndrome (and this diagnosis should be considered in a young patient presenting with fast AF), intravenous flecainide is an alternative for attempting pharmacological cardioversion, and atrioventricular node-blocking agents (such as diltiazem, verapamil, or digoxin) should not be used.

Rhythm control

The approach to rhythm control in AF is often guided by the presence of associated structural heart disease. All anti-arrhythmic drugs have side-effects (see Table 4), and in some cases (e.g. Class I and III agents), pro-arrhythmia may be precipitated. Pro-arrhythmias can be serious (such as torsade des pointes) and the risk is exacerbated by electrolyte abnormalities (hypokalaemia, hypomagnesaemia), drugs (tricyclic antidepressants, macrolide antibiotics), and structural heart disease (cardiac ischaemia, left ventricular hypertrophy, impaired cardiac function, etc.). Thus, a stepwise approach to rhythm control is sometimes advocated, with less efficient (but probably safer) drugs advocated as first-line, and stronger anti-arrhythmia agents (with more adverse effects and risk of pro-arrhythmia) reserved if first-line agents are ineffective or not tolerated. In all cases, appropriate anti-thrombotic therapy should be used (see later).

In paroxysmal AF, beta-blockers are often used as first-line to suppress paroxysms of AF, as they are relatively good and have an acceptable drug side-effect profile. In the absence of structural heart disease, a Class Ic agent (e.g. flecainide, propafenone) is the next option, whilst amiodarone (Class III) is used where structural heart disease is present. Digoxin may be detrimental in paroxysmal AF, resulting in an increased frequency of paroxysms, although the rate may be somewhat controlled should paroxysms occur.

In persistent AF, restoration of sinus rhythm may be achieved by anti-arrhythmic agents (usually Class I and III agents), or by electrical cardioversion. To improve chances of successful cardioversion, patients are often started on these drugs pre-cardioversion, and, following successful restoration of sinus rhythm, this is often maintained by continued use of the same anti-arrhythmic agent. Digoxin is no better than placebo for cardioversion, and should not be used.

There are also non-pharmacological approaches to rhythm control for paroxysmal and persistent AF. In many instances where medical therapy has failed, patients generally have had great symptomatic improvement after an electrophysiological intervention.

Rate control

A rate control strategy is advocated in permanent AF. For rate control, the best initial drugs to use are beta-blockers or rate-limiting calcium antagonists (verapamil, diltiazem), and, if necessary, as combination therapy with digoxin. Digoxin monotherapy only controls the heart rate at rest, and is less effective at rate control during exercise or in

History

- Symptoms and severity
- Effect on activities of daily life
- Risk factors
- Drugs including adverse effects

Clinical examination

- Rate (pulse and apex)
- Cardiac murmurs and rubs

12-Lead ECG

- Confirm diagnosis
- Rate
- Exclude other arrhythmias
- Look for pre-excitation syndromes
- Voltage for left ventricular hypertrophy
- Look for signs of IHD

Chest X-ray

- For chronic lung diseases
- Lung tumours

Blood tests

- Full blood count
- Electrolytes
- Thyroid function tests

Echocardiogram

- Structural heart diseases
- Valvular disease
- Left atrial size
- Left ventricular size and function
- Pericardial disease

Holter/other cardiac monitoring

- For rate control assessment
- For paroxysmal disease diagnosis confirmation

Exercise tolerance test

- Exercise-induced AF diagnosis
- Exercise rate control assessment

TABLE 3 Assessment of the patient with AF.

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Anti-arrhythmic drugs in AF	Common adverse effects
Class Ia	
Procainamide*	Lupus-like syndrome, gastrointestinal symptoms, torsade de pointes
Quinidine	Congestive heart failure, ventricular tachycardia, enhanced AV nodal conduction (conversion to atrial flutter)
Disopyramide	Heart failure, urinary retention, dry mouth, glaucoma, torsade de pointes
Class Ic	
Flecainide* Propafenone*	Congestive heart failure, ventricular tachycardia, enhanced AV nodal conduction (conversion to atrial flutter)
Class III	
Amiodarone*	Photo sensitivity, hepatotoxicity, pulmonary toxicity, gastrointestinal symptoms, bradycardia, thyroid dysfunction, polyneuropathy, rarely torsade de pointes
Sotalol	Congestive heart failure, torsade de pointes, bradycardia, exacerbation of chronic obstructive airways disease, or asthma
Ibutilide*	Ventricular tachycardia, torsades de pointes

TABLE 4 Anti-arrhythmic drugs in AF. *Intravenous preparations available for acute AF.

conditions of high sympathetic drive (e.g. fever, heart failure). Some elderly, sedentary patients with AF have a slow ventricular rate and may not need additional rate control drugs. In all cases, appropriate antithrombotic therapy should also be used (see later).

It should be emphasised that rate control is not an inferior strategy to rhythm control for AF, and in recent trials fewer adverse drug reactions and hospitalisation episodes have been noted in patients assigned for rate control. In a recent analysis of functional status with rate or rhythm control from the AFFIRM trial, the NYHA-functional class worsened with time in both rate control and rhythm control groups, with no differences seen between groups; however, the presence of AF was associated with a worse NYHA-functional class. The six-minute walk distance was 94 feet greater in the rhythm-control group compared with those managed with rate control (adjusted p value = 0·049).

ANTITHROMBOTIC THERAPY

Antithrombotic therapy is a well-established part of AF management to reduce the risk of stroke and thromboembolism. In a recent meta-analysis of 13 trials (n=14,423 participants) of antithrombotic therapy in AF, adjusted-dose warfarin reduced the risk of ischaemic stroke or thromboembolism compared with placebo (RR 0·33; 95% CI: 0·24 to 0·45). The risk reduction in total stroke was similar with primary and secondary prevention (RRR 59% vs 68%) the absolute risk reduction for all stroke was far greater for secondary stroke prevention (8·4% per year; NNT for one year to prevent one stroke 12) when compared with primary prevention (2·7% per year; NNT 37). Furthermore, oral anticoagulation therapy reduced all-cause mortality (RR 0·69; 95% CI: 0·53 to 0·89). Of note, adjusted-dose warfarin was also superior to aspirin in reducing the risk of ischaemic stroke or thromboembolism (RR 0·59; 95% CI: 0·40 to 0·86).

In the BAFTA clinical trial, Mant *et al.*[6] recently assessed whether warfarin (INR2-3) reduced the risk of major stroke, arterial embolism, or other intracranial haemorrhage compared with aspirin 75 mg in 973 elderly (aged >75) AF patients. There were fewer primary events in patients on warfarin compared to those assigned to aspirin (RR 0·48, 95% CI 0·28 to 0·80). This contemporary clinical trial supports the use of anticoagulation therapy for elderly people with AF.

Aspirin significantly reduces the risk of stroke by 22% (95% CI 2–38%), with no statistically significant increase in the risk of major haemorrhage. Aspirin leads to an absolute stroke risk reduction of 1·5% a year for primary prevention and 2·5% per year for secondary prevention (NNT of 67 and 40, respectively). It is likely that the effect of aspirin on stroke reduction in AF may simply reflect the effect on vascular disease, rather than AF *per se*, as the relative risk reduction of stroke by aspirin compared to placebo of 22% is similar to the stroke risk reduction (22%) seen for the use of antiplatelet therapy in high risk vascular disease patients in the Antithrombotic Trialists' Collaboration.

Another antiplatelet agent, clopidogrel, has been used in clinical practice in patients who are unsuitable for warfarin, and intolerant to aspirin. The recent ACTIVE trial reported that warfarin anticoagulation was still superior to aspirin–clopidogrel combination therapy in moderate- to high-risk patients with AF participating in the ACTIVE-W arm of the study. This trial (which was stopped early due to the superiority of the warfarin arm) reported rates of vascular events (defined as stroke, embolism, myocardial infarction, and vascular death) that were significantly higher in the aspirin–clopidogrel-treated patients (5·64% per year) than in the warfarin arm (3·63% per year); a difference of 1·7% per year (RR 1·45, p=0·0002). Major bleeding events, however, were similar, at 2·4% per year and 2·2% per year (RR 1·06, p=0·67) respectively.

Nonetheless, the stroke risk in AF is not homogeneous, and many risk stratification schemes have been proposed, as recently reviewed by Lip and Boos.[1] One suggested risk stratification scheme and guideline for thromboprophylaxis is shown in Figure 1, which offers a balance between evidence, practicality, and applicability.

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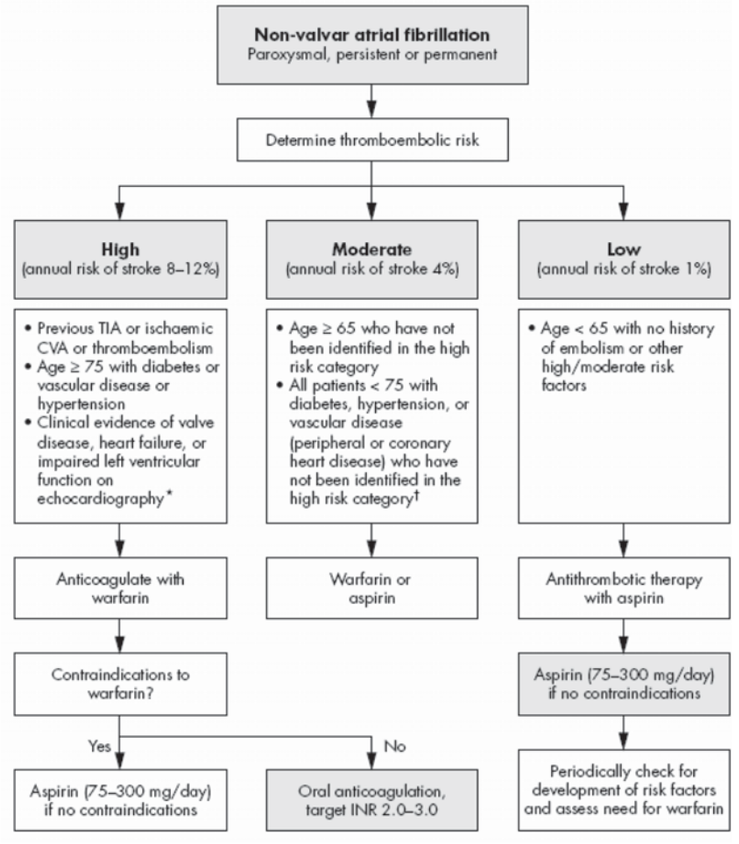

FIGURE 1 Practical guidelines for antithrombotic therapy in non-valvular atrial fibrillation.[9] Assess risk, and reassess regularly. Note that risk factors are not mutually exclusive, and are additive to each other in producing a composite risk.
An echocardiogram not needed for routine risk assessment but refines clinical risk stratification in case of moderate or severe left ventricular dysfunction and valve disease.
*Since the incidence of stroke and thromboembolic events in patients with thyrotoxicosis appears similar to other aetiologies of AF, antithrombotic therapies should be chosen based on the presence of validated stroke risk factors.
†Owing to lack of sufficient clear-cut evidence, treatment may be decided on an individual basis, and the physician must balance the risks 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 risk factors. Referral and echocardiography may help in cases of uncertainty.

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Nonetheless, one increasing management problem is what to do when an anticoagulated AF patient (usually in the 'high risk' stroke strata) has associated vascular disease (coronary, carotid and/or peripheral artery disease). Common practice is to add aspirin to warfarin, but such an approach does not reduce stroke or vascular events, but increases bleeding.[7] Furthermore, if such an AF patient presents with ACS and/or requires percutaneous coronary intervention with stenting – especially if a drug eluting stent is used – combination antiplatelet therapy with aspirin plus clopidogrel is recommended, but giving this combination with warfarin would substantially increase the risk of bleeding. Given the lack of clinical trial data, a management approach that balances stroke prevention against cardiac events (stent thrombosis, recurrent ACS) and bleeding risk is needed.[8]

NON-PHARMACOLOGICAL APPROACHES

A detailed treatise on the non-pharmacological approaches to the management of AF are beyond the scope of this article. For example, several surgical procedures for arrhythmia surgery are available and the Maze procedure (Cox–Maze III operation) has been reported to eliminate AF in approximately 90% of cases; however, this is very complex and a major surgical procedure and new methods of perioperative catheter ablation are increasingly used.

The pulmonary veins are thought to be the focal source of AF generation and percutaneous catheters are used to isolate the pulmonary veins using radiofrequency energy delivered via the tip of the catheter. In a recent small, randomised trial, PVI with radiofrequency ablation was compared with anti-arrhythmic drugs as initial management for symptomatic AF. This trial found that PVI patients had better outcomes in terms of AF recurrences and hospitalisations after one year of follow-up, as well as a better quality of life at six months. Enthusiasm for this approach needs to be tempered by another recent study,

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which reported that during the six-month follow-up period, only 54% and 82% of patients remained free of arrhythmia-related symptoms after circumferential pulmonary vein ablation and after segmental pulmonary vein ablation, respectively. Indeed, asymptomatic episodes may occur and significantly increase after catheter ablation amongst previously symptomatic patients: thus, follow-up based on symptoms only would substantially overestimate the success rate of ablation procedures. Although more data are awaited, PVI may perhaps be considered for patients who were resistant to pharmacological treatment, especially those who are younger and have lone AF. Generally, paroxysmal AF has better success than persistent AF, and underlying structural heart disease reduces the success rate.

In some patients with permanent AF resistant to medical therapy for rate control, atrioventricular nodal ablation and permanent pacemaker implantation is an option. In these cases, the atria continue to fibrillate hence the atrioventricular synchrony is not restored, and the risk of stroke does not decrease, necessitating anticoagulation.

THE FUTURE

There is increasing interest in the role of the RAAS in AF and increasing data point towards the benefits of ACE inhibitors and angiotensin-receptor blockers in the setting of AF. Part of this benefit may be modulation of inflammation and the prothrombotic state, which is evident in AF, which may account for the benefits of drugs such as statins and omega-3 fatty acids. In addition, warfarin and other vitamin K antagonists have the inconvenience of variable dosing, anticoagulation monitoring, and food/drug interactions. These disadvantages of warfarin may well be overcome by new oral anticoagulants, which act by direct thrombin inhibition or by Factor Xa inhibition. New anti-arrhythmic drugs are also in development, as are novel electrophysiological interventions that may hold the promise of a viable alternative to medical therapies for AF.

KEYPOINTS

- Atrial fibrillation is a common cardiac arrhythmia, with a substantial mortality and morbidity.
- Atrial fibrillation has been classified clinically on the basis of presentation, and such clinical subtypes may help the approach to management as it defines the objective of therapeutic intervention.
- Any treatment strategy should be aimed not only at treating AF, but also at treatment or management of the underlying co-morbidities (especially hypertension), correctable precipitants (e.g. thyroid disease), structural heart disease, or pulmonary disease.
- Antithrombotic therapy is a well-established part of AF management to reduce the risk of stroke and thromboembolism. Risk stratification is an essential part of thromboprophylaxis management.
- Non-pharmacological approaches to managing AF, such as PVI, are increasingly considered.

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