Treatment of atrial fibrillation

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Introduction: Atrial fibrillation (AF) is the most common, sustained rhythm disturbance. The prevalence of AF is increasing as people live longer. Common conditions such as hypertension and ischaemic heart disease play an important role in the development of AF. The presence of AF is associated with increased morbidity and mortality from stroke and heart failure, particularly in patients with structural heart disease.

Sources of data: This article provides evidence-based information on the key aspects of managing AF which is based on major guidelines, landmark clinical trials and meta-analyses.

Areas of agreement: It is well recognized that both rate control and rhythm control are important strategies for the management of AF, but each approach should be chosen according to individual patient circumstances. A vast majority of elderly, relatively asymptomatic patients will benefit from ventricular rate control. Embolic stroke remains a major complication of AF. Yet, anticoagulation with warfarin remains underprescribed, especially in the elderly due to the presumed risk of bleeding. The technique of catheter ablation continues to improve and is generally successful in younger patients with relatively normal hearts.

Areas of controversy: There are clinically relevant differences among published schemes designed to stratify stroke risk in patients with AF. The CHADS2 score is currently the most simple system to give some initial estimate of stroke risk in AF patients, but could significantly underestimate this risk, particularly in those who fall in the ‘intermediate’ risk category.

Growing points and areas timely for developing research: Novel antiarrhythmic agents, including atrial specific agents with improved efficacy and safety profile, are currently under development. New antithrombotic agents with efficacy similar to warfarin which do not require regular INR testing appear to be promising, but there are lack of data about their long-term safety. There is increasing evidence that inflammation and fibrosis may play a major role in the initiation and maintenance of AF. Statins by means of their pleotropic effects and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers by preventing atrial remodelling may prove useful in preventing the
development of AF. However, there is insufficient evidence to expand the use of these agents to a wider patient population at risk of AF. It needs to be seen if strategies towards primary and secondary prevention with treatment of underlying heart disease and modification of risk factors have a larger effect than specific interventions in preventing the burden of AF in the general population.

*Keywords:* atrial fibrillation/rate control/rhythm control

### The burden of atrial fibrillation

Atrial fibrillation (AF) affects about 1.5% of the UK general population, the prevalence rising to 5% beyond the age of 65 years and 10% in those over 75 years.\(^1\) The Framingham Study in the USA and the Rotterdam Study in Europe have estimated lifetime risk for development of AF to be one in four for men and women 40 years of age and older. Men are 1.5 times more likely to develop AF.\(^2,3\) Projected data from two population-based studies in the USA (California and Minnesota) predict a 2.5–3-fold upsurge in the number of patients with AF by 2050.\(^4,5\) The majority of surveys and epidemiological studies have reported the incidence of AF in a white population. The prevalence and incidence of AF in non-white populations is less well studied, but lower values were reported for Asians and Afro-Americans.\(^6\) In the health survey of 664 754 US veterans, the age-adjusted prevalence was 5.7% in whites, 3.4% in blacks, 3.0% in Hispanics, 5.4% in native Americans/Alaskans, 3.6% in Asians and 5.2% in Pacific Islanders.\(^7\) Racial differences remained after adjustment for age, body mass index and these co-morbidities. White men were significantly more likely to have AF compared with all races but Pacific Islanders (odds ratios versus blacks, 1.84; versus Hispanics, 1.77; versus Asians, 1.41; versus Native Americans, 1.15; \(P < 0.001\)).

The number of patients with AF is likely to increase 2.5-fold during the next 50 years, reflecting the growing proportion of elderly individuals many of whom have survived cardiovascular diseases that would have proved fatal in previous times. Much AF is relatively asymptomatic until complications arise. The increased use of electrocardiograms and examination of the pulse during routine health checks has revealed that almost as many elderly patients have the silent form of AF as are symptomatic with this arrhythmia. AF may be paroxysmal when episodes last <7 days. The majority of patients presenting with AF < 72 h duration spontaneously convert to sinus rhythm.\(^8\)

Although AF is classically caused by hypertension, heart failure, myocardial infarction, mitral stenosis, thyrotoxicosis and alcohol, previously
unrecognized risk factors, such as obesity, metabolic syndrome, diastolic dysfunction, sleep apnoea, psychological stress, and tall stature, have emerged. Genetic predisposition to AF or specific genetically predetermined forms of the arrhythmia have also been described.

The presence of AF is associated with increased morbidity and mortality, particularly in patients with structural heart disease.

The most serious complications of AF are stroke and heart failure. In the Framingham study, the risk of stroke increased from 1.5% for AF patients aged 50–59 years to 23.5% for those between 80 and 89 years. The presence of heart failure, concomitant coronary disease, hypertension, metabolic disease, use of class III antiarrhythmic drugs and hospitalizations are the major determinants of AF treatment costs. AF and its associated morbidity represent a significant socio-economic burden on the healthcare system consuming between 0.9% and 2.4% of total NHS expenditure in the UK. In-patient care and interventional procedures appear to be the main drivers of overall cost in Europe.

Thus, it is vital to adopt an effective strategy to prevent or treat this most common, sustained rhythm disturbance which was once considered benign.

The following review focuses on current pharmacological and non-pharmacological strategies in the management of AF.

The onset and maintenance of atrial tachyarrhythmias

The exact electrophysiological mechanisms of initiation and maintenance of AF remain controversial. AF appears to be a micro re-entrant arrhythmia with multiple wavelets and daughter wavelets randomly colliding with each other. Factors such as persistent tachycardia, valvular diseases, myocardial ischaemia, systemic hypertension and diastolic dysfunction lead to excessive pressure or volume overload on the left atrium which responds with various time-dependent adaptive processes. Structural, functional, electrical and metabolic consequences eventually lead to permanent remodelling and dilatation. These responses include atrophy or hypertrophy of atrial myocardial fibres, age-related degenerative changes with increase in fibrous tissue and senile amyloidosis and are associated with genesis of atrial ectopics, paroxysmal AF or atrial tachycardia (AT), which eventually results in chronic AF or atrial flutter (AFL) (Fig. 1). The majority of AF originates from the left atrium. Recent evidence shows that ‘sleeves’ of atrial tissue extend into the pulmonary veins are frequently involved in the initiation of atrial arrhythmias (the basis of pulmonary vein isolation procedure for termination of AF). AFL represents a more
organized form of re-entrant circuit and unlike AF, generally arises predominantly from the right atrium. There is a close interrelationship between AF and AFL. AF of variable duration generally precedes the onset of AFL. On the other hand, fast AFL can degenerate into fibrillatory conduction and maintain AF. Pharmacological management of AFL in terms of rhythm or rate control and thromboprophylaxis is similar to that of AF.

Current treatment strategies are aimed at preventing recurrence of AF and its complications, such as stroke and heart failure. However, primary prevention strategies targeting the most prevalent risk factors, such as hypertension, obesity and ischaemic heart disease, are likely to have a major impact on reducing the burden of AF.

Classification of AF

The most widely accepted classification of AF is based on its temporal pattern of occurrence. First detected AF is the first clinical presentation, the onset of which may be unknown. Paroxysmal AF is a recurrent form that typically lasts for minutes to hours, occasionally days (not more than 7), but eventually self-terminates. Persistent AF is present when arrhythmia has lasted for more than 7 days, does not self-terminate and pharmacological or electrical cardioversion is required to restore sinus rhythm. Included within the category of persistent AF is ‘longstanding persistent AF’ which is defined as continuous AF of >1 year duration. AF is
regarded as *permanent* when all attempts to restore sinus rhythm have been abandoned due to physician or patient decision, frequent recurrence or inability to cardiovert the patient. As our experience with newer anti-arrhythmic drugs (AAD) and invasive ablation techniques continues to improve, there is an increasing trend to treat AF in patients who previously would have been classified as ‘permanent’.19

**Treatment of acute onset AF**

The main aspects of managing AF are:

(i) urgent control of the ventricular rate during paroxysmal or persistent AF;

(ii) restoration of sinus rhythm by pharmacologic or electrical means;

(iii) prevention of recurrence of AF following successful restoration of sinus rhythm;

(iv) long-term rate control in those with permanent AF;

(v) prevention of thromboembolic complications.

In an emergency setting, the priority is to maintain haemodynamic stability which can be achieved either by urgently restoring sinus rhythm or by controlling the ventricular rate in a patient with AF presenting with a fast heart rate. Rapid control of ventricular rates in stable patients can be achieved by intravenous or oral atrioventricular (AV) nodal blocking agents (beta-blockers, digoxin and non-dihydropyridine calcium channel blockers—verapamil and diltiazem). Target resting heart rate of $<100$ bpm is considered as adequate control.20 Diltiazem is less negatively inotropic with less potent effects on peripheral vasculature than verapamil and may be the preferred intravenous agent during acute situations. In patients who have high adrenergic tone (e.g. inflammation, post-operative AF and myocardial ischaemia), intravenous beta-blockers (e.g. metoprolol, propranolol and esmolol), as opposed to digoxin, are particularly useful through their sympatholytic properties. Intravenous digoxin is the drug of choice for rate control in AF patients presenting with heart failure due to its positive inotropic and negative chronotropic effects. Urgent direct-current cardioversion (DCC), irrespective of the duration of AF, is indicated in patients who are haemodynamically unstable or have clinical signs of life-threatening myocardial ischaemia or heart failure. If DCC is not urgently available, amiodarone or digoxin can be given parenterally. Amiodarone is more effective than digoxin by initially providing rapid rate control due to its action on the AV node, followed by cardioversion to sinus rhythm. Intravenous use of digoxin, diltiazem, verapamil and beta-blockers is contraindicated when AF is associated with an accessory pathway, such as in the Wolff–Parkinson–White syndrome.
(pre-excited AF). Intravenous flecainide, procainamide, disopyramide, ibutilide or amiodarone are preferable in such circumstances.\textsuperscript{21}

**Pharmacological cardioversion**

Up to 50\% of patients with new onset AF spontaneously convert to sinus rhythm within 24–48 h. AF associated with chest infections and electrolyte disorders usually settles with adequate treatment of the primary disorder, but may require elective cardioversion if it persists. If AF is of recent onset (<7 days) and the patient is haemodynamically stable, pharmacological cardioversion can be effective. Class IC agents, such as intravenous or oral flecainide or oral propafenone, are commonly used for terminating acute-onset AF in stable patients. These agents act within minutes when given intravenously or several hours if given orally. Amiodarone, in contrast, achieves cardioversion much more slowly by oral or intravenous routes.\textsuperscript{22} Usually, class IC agents are avoided in the elderly in favour of amiodarone due to the possibility of co-morbidities such as coronary artery disease and left ventricular dysfunction. Class III agents such as ibutilide (not available for use in the UK) have high success rates in cardioverting AFL but are less useful for cardioversion of AF. Intravenous ibutilide has shown higher success in cardioverting AFL (65–80\%) than AF (35–50\%).\textsuperscript{23} When the arrhythmia has persisted more than a week, Class III agents may be more effective than IC drugs.

Table 1 gives an overview of drugs with proven efficacy for cardioversion of recent onset AF and those effective for maintenance of sinus rhythm.

All patients should be anticoagulated using heparin and subsequently with warfarin, if AF has persisted for >48 h, if cardioversion (pharmacological or electrical) is anticipated or if the patient is at risk for thromboembolism. It is often difficult to ascertain the exact duration of AF even when the patient presents acutely. Long-term continuation of oral anticoagulation (discussed below) is guided by the presence of risk factors for thromboembolism and does not depend on the frequency or duration of paroxysms.

**Pharmacological maintenance of sinus rhythm**

Most AAD which are useful for acute pharmacological cardioversion of AF can also be used orally for long-term maintenance of sinus rhythm. Amiodarone stands superior to other agents in maintaining sinus rhythm after cardioversion.\textsuperscript{24} Chronic use of amiodarone,
Table 1 Drugs used for cardioversion of recent onset AF and those effective for maintenance of sinus rhythm

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route for acute conversion</th>
<th>Rhythm maintenance</th>
<th>Rate control</th>
<th>Contraindicated if LVH or LV dysfunction</th>
<th>Proarrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents with proven efficacy for acute conversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Oral</td>
<td>Yes</td>
<td>No</td>
<td>No (second choice)</td>
<td>Prolongs QT/TdP</td>
</tr>
<tr>
<td>Flecainide</td>
<td>IV or oral</td>
<td>Yes</td>
<td>No</td>
<td>Yes*</td>
<td>†QRSD/VT/facilitate AV conduction</td>
</tr>
<tr>
<td>Propafenone</td>
<td>IV or oral</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Low incidence of TdP/multiorgan toxicity</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>IV or oral</td>
<td>Yes</td>
<td>Yes</td>
<td>No (first choice)</td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td>IV or oral</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>†QRSD/VT</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IV</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>†QRSD/VT</td>
</tr>
<tr>
<td>Sotalol</td>
<td>(Oral or IV)†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Prolongs QT/TdP</td>
</tr>
</tbody>
</table>

IV, intravenous; TdP, torsades de pointes; QRSD, QRS duration; QT, QT interval; VT, ventricular tachycardia (monomorphic); AV, atrioventricular.

*Also contraindicated in coronary disease.
†Not primarily used for acute conversion.

however, is limited by side effects which include bradycardia, photosensitivity, thyroid dysfunction, liver toxicity and visual disturbances.  

These drugs may improve the success rates of elective CV but may need to be prescribed for several weeks prior to the procedure to provide optimal effect. Drugs commonly used in the UK to prevent future paroxysms are conventional beta-blockers, class IC agents (flecainide and propafenone) and class III agents (sotalol and amiodarone). Standard beta-blockers have shown modest efficacy in maintaining sinus rhythm when compared with placebo or sotalol, and should be considered prior to use of Class IC and class III agents to prevent paroxysms since there is lesser risk of drug-related pro-arrhythmia.  

Class IC agents are contraindicated in the presence of ischaemic heart disease and/or ventricular dysfunction because of their negative inotropic and proarrhythmic effects. Sotalol is best avoided in those with heart failure or ventricular hypertrophy (or depressed renal function) due to increased risk of QT prolongation and proarrhythmia (Fig. 2).

Since ischaemic heart disease and myocardial dysfunction are common in the elderly, amiodarone generally becomes the drug of preference in such situations. Amiodarone is also associated with potentially dangerous prolongation of the QT interval, although less commonly than with sotalol, regular monitoring of the QT interval...
Fig. 2 Prolongation of QT interval in a patient receiving sotalol that led to polymorphic ventricular tachycardia (torsades de pointes).

(and QRS duration with class IC agents) on the 12-lead ECG is important during outpatient review.

Patients with infrequent and brief paroxysms of AF need not require regular therapy or may be controlled on low doses of antiarrhythmic agents and may be best suited for the strategy of suppressing the arrhythmia by taking a single dose or an extra dose of the antiarrhythmic medication (class IC agents, flecainide or propafenone) at the time of experiencing a paroxysm (the ‘pill-in-the-pocket’ approach). This approach, however, is usually reserved for those with a structurally normal heart, absence of bundle branch blocks, normal resting heart rate and blood pressure and an understanding of how and when to take the extra medication. Since bradycardia may be profound immediately following cardioversion with class IC drugs, the ‘pill-in-the-pocket’ approach should first be tested in hospital under close monitoring. Moreover, class IC drugs can initiate AFL and facilitate rapid conduction via the AV node during AF; these agents are best given in combination with beta-blockers or calcium channel blockers.

Role of statins, ACE inhibitors and angiotensin receptor blockers on recurrence of AF

It appears that primary and secondary prevention of AF with ‘upstream’ therapy (i.e. treating underlying heart disease) and risk factor modification is likely to produce a larger effect in the general population than will specific interventions.28

There is increasing evidence that inflammation and fibrosis may play a major role in initiation and maintenance of AF. Inflammatory markers, interleukin-6 and C-reactive protein, are raised in AF and correlate with the duration of AF, success of cardioversion and thrombogenesis. Statins may affect the natural history of AF by means of their ‘pleotropic effects’ which are independent of their lipid lowering effect, whereas ACE-I and ARBs prevent atrial remodelling via suppression of renin–angiotensin system (RAS) (Table 2).29,30 Meta-analysis of six randomized controlled studies in 3557 patients has shown that the use of statins was associated with a 61% reduction in the incidence of recurrent AF.29
Recently, activation of RAS has been recognized as a key element in atrial remodelling. Angiotensin II produces a variety of direct and indirect effects on structure and electrophysiologic properties of the atria. It may stimulate atrial fibrosis and hypertrophy, promotes inflammation, uncouples cell-to-cell communication and impairs calcium handling. Meta-analysis of several retrospective reports as well as prospective studies in patients with congestive heart failure and hypertension has reported that therapy with ACE inhibitors and angiotensin receptor blockers reduced the risk of new onset AF by 20–30%. Furthermore, the results of prospective studies of secondary prevention of AF have uniformly demonstrated a significant reduction in AF recurrence after electrical cardioversion, if patients were treated with ACE inhibitors or an angiotensin receptor blockers in addition to amiodarone. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial in 15 000 hypertensive patients at high cardiovascular risk, new onset AF was less frequent in the valsartan-treated group than with the amlodipine-based regimen. The Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity trial (CHARM) which included AF as a pre-specified endpoint showed a 19% reduction in the incidence of new onset AF in patients with congestive heart failure and an ejection fraction of <40% compared with placebo.

However, despite supporting evidence from animal experiments, positive outcomes from observational studies and post hoc analyses in selected patient categories, there is insufficient evidence to warrant a recommendation to expand the indications in a wider patient population at risk of AF.

**Rate versus rhythm control**

Several recent studies comparing rhythm versus rate control have shown no significant differences between the two strategies in terms of mortality from cardiovascular causes and stroke.
There was a non-significant trend towards increased mortality in the rhythm-control group in the AFFIRM trial. Further sub-analysis of data from these studies has revealed that use of AADs was independently associated with increased mortality (due to ischaemic stroke in those with recurrence of AF in the absence of anticoagulation, or from proarrhythmia) highlighting the poor efficacy and safety of the current agents. Nevertheless, in symptomatic patients, maintenance of sinus rhythm appears to improve exercise capacity and measures of quality of life. The most appropriate initial treatment strategy depends on individual patient circumstances and co-morbid conditions. Most patients in these studies were between 60 and 70 years of age and the results are not necessarily applicable to those in younger age groups who have less overall risk of ischaemic stroke and would benefit from maintaining sinus rhythm. In patients with heart failure (left ventricular ejection fraction <50%), rhythm control appeared to be associated with a better outcome in terms of mortality, but in a recent larger study (AF-CHF), outcomes were similar between rhythm and rate control strategies, although it is possible that deleterious proarrhythmic effects of AADs could have negated the beneficial effects of maintaining sinus rhythm. The study showed no benefit of rhythm control (mainly amiodarone-based regimen) on top of optimal medical therapy on cardiovascular death (the primary endpoint) as well as pre-specified secondary endpoints (total mortality, worsening heart failure, stroke and hospitalization). Cardiovascular death occurred in 26.7% of the patients in the rhythm control group compared with 25.2% in the rate control arm (hazard ratio 1.058, \( P = 0.59 \)). Table 3 summarizes the patient suitability for the two strategies based on evidence from recent trials. The decision to adopt either strategy as a long-term goal will usually depend on patient choice, symptoms, age, the risk–benefit ratio of chronic therapy (efficacy versus proarrhythmia, negative inotropism and non-cardiac side effects) and on factors that predict future recurrences of AF (Box 1).

<table>
<thead>
<tr>
<th>Table 3 Factors favouring rate or rhythm control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rhythm control</strong></td>
</tr>
<tr>
<td>Symptomatic patients</td>
</tr>
<tr>
<td>Younger age group</td>
</tr>
<tr>
<td>Presence of lone AF</td>
</tr>
<tr>
<td>AF secondary to known precipitant cause (e.g. thyrotoxicosis, chest infection, alcohol and excessive caffeine intake)</td>
</tr>
<tr>
<td>Presence of heart failure (controversial)</td>
</tr>
</tbody>
</table>
Factors predicting recurrence of AF

Failed attempts at cardioversion
AF duration > 1 year
Enlarged left atrium
Ventricular dysfunction
Valvular dysfunction (especially mitral)

Rate control in permanent AF

Criteria for adequate rate control AF are solely based on the overall ventricular rates assessed using 12-lead or ambulatory ECG recordings and do not currently take into account irregularity of the ventricular response, quality of life, symptoms or development of cardiomyopathy. Optimal control of the ventricular rate is necessary to reverse development of cardiomyopathy and improve left ventricular stroke output. Tachycardia-induced cardiomyopathy tends to resolve within 6 months of rate control, but re-develops rapidly when fast AF recurs and carries a poor prognosis. What should be the adequate heart rate in AF itself remains controversial. Heart rate should neither be too high (leads to reduction of exercise tolerance and development of tachycardia-induced cardiomyopathy) nor too slow (leads to reduced exercise tolerance, dizziness, pre-syncope, etc). AF is generally considered to be well controlled when the ventricular rate at rest is 60–80 and 90–115 bpm during exercise, although less strict criteria (<100 bpm at rest and <115 bpm during exercise) are also used. Long-term rate control is achieved by drugs which predominantly affect conduction through the AV node. Commonly used agents are digoxin, beta-blockers and non-dihydropyridine calcium channel blockers, verapamil and diltiazem. In permanent AF, digoxin usually provides adequate rate control at rest, but does not prevent excessive heart rates during exercise or other high adrenergic states such as fever, thyrotoxicosis, volume loss or following surgery, and is best reserved for sedentary patients. Since high sympathetic tone is usually a precipitant in paroxysmal AF, digoxin is unlikely to be effective in these patients. In contrast, in patients with reduced left ventricular function, digoxin modestly improves heart rates and is the drug of choice in heart failure. In suitable patients, beta-blockers or non-dihydropyridine calcium antagonists are given as monotherapy as first-line agents for rate control. Combination therapy using digoxin with a beta-blocker or calcium antagonist is often necessary for adequate rate control. Combination therapy also minimizes the occurrence of side effects arising from high
doses of single agents. If such combinations are ineffective, an oral beta-blocker may be used together with diltiazem (less negatively inotropic and less vasoactive than verapamil) or amiodarone may be used in selected patients for its powerful AV nodal blocking properties. Sotalol, although primarily prescribed as an AAD, also controls the ventricular rate at higher doses (240 mg daily) and reduces symptoms during paroxysms.

In the elderly, AF frequently co-exists with degenerative involvement of the conduction system (sick sinus disease or AV block) and caution must be exhibited when using AV nodal blocking agents. Such patients usually require support from a permanent pacemaker to allow use of combinations or higher doses of these drugs. Permanent pacing also becomes necessary when it is difficult to control the fast ventricular rate, despite drug therapy. There is an option to completely block the AV conduction by radiofrequency or cryo ablation of the AV node followed by the implantation permanent ventricular pacemaker.

**Stroke prevention and antithrombotic therapy in AF**

In AF, the risk of peripheral thromboembolism remains significant and increases with age from 1.5% in patients <60 years to >24% in those over 80 years of age, regardless of paroxysmal, persistent or permanent AF. The rate of ischaemic stroke in AF is independently related to increasing age and coexistent cardiovascular disease with a history of prior stroke being the strongest predictor.

Warfarin remains underprescribed in clinical practice. More than 40% of those at high risk of thromboembolism may not be receiving adequate anticoagulation, particularly the most vulnerable group, the elderly and institutionalized patients, who are denied anticoagulation on the basis of a presumed increased risk of haemorrhagic complications.

All patients with AF lasting >48 h who are selected for elective cardioversion require at least 3 weeks of adequate anticoagulation (INR of 2.5; range 2.0—3.0) regardless of what method of cardioversion is employed.

In practice, this usually involves anticoagulating patients until well-controlled INR values between 2.0 and 3.0 have been achieved for 3–4 weeks. In selected patients, pre-cardioversion transoesophageal echocardiography (TOE) can be used to exclude the presence of intra-atrial thrombi or spontaneous echo-contrast (increased viscosity of blood prior to thrombus formation seen as smoke-like appearance on echo). Patients with confirmed AF of <48 h duration have the least risk of thromboembolism during cardioversion and can be safely cardioverted.
with heparin cover without the need for transthoracic echocardiography or TOE. The atria remain ‘stunned’ and may not achieve full mechanical function for several days following electrical cardioversion, despite the presence of P waves on the surface ECG. Unless contraindicated, all patients subjected to DCC and those with AF >48 h duration require at least 4 weeks of full anticoagulation (INR 2.0–3.0) in the post-cardioversion period.

Long-term continuation of antithrombotic therapy with anticoagulant or antiplatelet agents is guided by the patient’s risk of thromboembolism and chances of AF recurrence. Risk stratification guidelines differ between various expert groups particularly for those falling in the 65–75 year age group. The CHADS2 risk stratification scheme combines elements from major expert groups and provides a well accepted, simple and practical way to assess stroke risk on a point system based on the established risk factors (Cardiac failure, Hypertension, Age >75, Diabetes and Stroke: 2 points) (Table 4).47,48

It should be acknowledged that new, improved and better-applied therapies in patients with risk factors produce better outcomes and are likely to reduce the absolute risk of stroke compared with historical controls.47

Antithrombotic therapy should be prescribed on an individual basis after assessing the risks and benefits of warfarin or aspirin. On the risk–benefit ratio, adjusted-dose warfarin is given to AF patients at moderate to high risk of thromboembolism (CHADS2 ≥2) with an aim to maintain a target INR of 2.5 (range 2.0–3.0). When the INR is >3.0, the risk of intracranial haemorrhage increases significantly. Patients at low risk (CHADS2 = 0), or those with contraindications or intolerance to warfarin, can be treated with 75–300 mg of aspirin (there is a lack of evidence regarding the dose of aspirin). Patients with a CHADS2 score of 1 may be treated with aspirin or warfarin. The decision is related to bleeding risk on the one hand (against warfarin) and the presence of less well-validated risk factors such as female gender, coronary artery disease, thyrotoxic basis for AF, etc. on the other.

<table>
<thead>
<tr>
<th>CHADS2 risk factor</th>
<th>Score</th>
<th>CHADS2 score</th>
<th>Annual stroke rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>1</td>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>1</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>2</td>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Score 0, low risk; 1–2, intermediate risk; and 3–6, high risk.
other (pro warfarin). The initiation of antithrombotic therapy depends on the presence or absence of risk factors for stroke and not on the maintenance of sinus rhythm or the frequency of paroxysms of AF. Antiplatelet combinations such as aspirin plus clopidogrel or aspirin plus dipyridamole are only acceptable in situations where warfarin cannot be given. The Stroke in AF Working Group (XX) performed a comparison of 12 published risk stratification schemes to predict stroke in patients with non-valvular AF and concluded that there were substantial, clinically relevant differences among published schemes designed to stratify stroke risk in patients with AF. The proportion of patients assigned to individual risk categories varied widely across the schemes. Those considered high risk ranged from 16.4% to 80.4%. The CHADS2 score categorized most subjects as moderate risk, classifying only about 20% of patients as high risk. This may have important clinical implications. For example, a patient with previous stroke and none of the other risk factors would be categorized as moderate risk. Clearly, previous stroke confers a significant risk of recurrent stroke (12% per year) and such patients warrant anticoagulation rather than aspirin. Nonetheless, especially given the observed rates of inadequate lack of oral anticoagulation in AF patients, the CHADS2 score is currently the most simple system to give some initial estimate of stroke risk in AF patients. Other, less validated, risk factors for stroke (such as coronary artery disease, female gender, thyrotoxicosis and age 65–74 years) and estimates of bleeding risk need to be applied with common clinical judgement to decide on optimal antithrombotic therapy in patients at ‘intermediate risk’ for stroke.49

Non-pharmacological techniques to prevent thrombus formation

In patients with AF, more than 90% of thrombi form in the left atrial appendage. Surgical closure or removal of the left atrial appendage has previously been tried, mainly in patients undergoing valve surgery. Newer techniques allow the percutaneous deployment of left atrial appendage transcatheter occlusion devices (e.g. Watchman®).

Catheter ablation of AF

Rhythm control of AF using non-pharmacological, percutaneous ablation techniques is becoming increasingly popular and may offer benefits over drug therapy in selected patients. Initial attempts
replicated the surgical Cox-Maze procedure by creating linear lesions in the atria using radiofrequency or cryo energy.\textsuperscript{50} Since the recent discovery of ectopic pulmonary vein foci that communicate with the left atrium through muscular sleeves, the technique has evolved to isolate these pulmonary vein triggers by creating circular lesions around the pulmonary veins.\textsuperscript{51} The ablation catheters are transvenously inserted into the right atrium and advanced into the left atrium via a transseptal puncture. The catheters are positioned to isolate or destroy electrical triggers (e.g. pulmonary vein foci and accessory pathways), abnormal atrial substrate that maintains AF (from electrical and structural remodelling, fibrosis and gap junction mutations) or autonomic innervations (ganglionated plexi around the pulmonary veins).\textsuperscript{52} Recent advances in three-dimensional imaging and electro-anatomical mapping techniques have improved catheter navigation, positioning and precise delivery of radiofrequency or cryo energy (Fig. 3).

The success rate of ablation varies with the type of AF. In patients with paroxysmal AF and relatively normal heart structure, elimination of arrhythmogenic pulmonary vein foci may achieve 80–90\% curative rates. Success is limited in those requiring ablation of the remodelling atrial tissue in persistent AF which requires isolation of both pulmonary veins and linear lines across the atrial substrate. Nevertheless, the overall success depends on appropriate selection of cases and the experience of

Fig. 3 Three-dimensional electroanatomical map of the left atrium viewed from the posterior aspect showing ablated areas encircling the four pulmonary veins.
the operators, and a large proportion of patients (10–40%) will require further attempts. Moreover, the technique is not without the risk of life-threatening complications, such as stroke, pericardial tamponade, proarrhythmia, pulmonary vein stenosis and rarely phrenic nerve injury and oesophageal fistula. Since long-term follow-up data are currently lacking, catheter ablation of AF is reserved for symptomatic patients who are resistant or intolerant to pharmacological therapy, particularly younger patients or those with heart failure.

As understanding of pathophysiology of AF improves, catheter ablation techniques could become first-line strategy if proven to be safer and more effective than pharmacological therapy.

The future

There are several new antiarrhythmic agents on the horizon that appear to be more efficacious and less toxic than the current drugs. Agents which have atrial selective actions and those targeting multiple ion channels are thought to be safer and free of ventricular proarrhythmic effects. Dronedarone is an amiodarone derivative that is devoid of the iodine moiety and appears to have a better side effect profile. In addition to its antiarrhythmic effect, dronedarone has been shown to reduce cardiovascular hospitalization or death from any cause (the composite primary endpoint) by 24% compared with placebo in >4000 high-risk patients with AF.

Celivarone, another amiodarone analogue, is under investigation. Celivarone has been shown to prevent recurrence of AF after electrical cardioversion, but the data are limited. Vernakalant is a relatively atrial-specific agent that predominantly delays atrial repolarization and may be devoid of proarrhythmic side effects. It is currently under consideration for pharmacological cardioversion of AF. Its oral formulation is being tested for prevention of post-cardioversion AF. Several other agents with novel actions such as gap junction modulators and atrial stretch inhibitors that prevent remodelling are currently under investigation.53

New antithrombotic agents with efficacy similar to warfarin but without the need of frequent INR testing also appear to hold future promise. Since thrombin plays a key role in propagation of thrombus formation, the safety and efficacy of orally administered direct and indirect thrombin inhibitors are also currently under investigation. Dabigatran, a direct thrombin inhibitor, which is in the final stage of development, appears promising as a replacement for warfarin.54 Long-acting parenteral factor Xa inhibitor (biotinylated idraparinux)
as well as several oral factor Xa inhibitors (e.g. rivaroxaban and apixaban) are under investigation for stroke prevention in AF.55

Conclusions

The prevalence of AF is rising as people live longer. Most of the disease appears to arise from other preventable cardiovascular illnesses such as hypertension, ischaemic heart disease and heart failure. Rate control and rhythm control are equally important strategies for the management of AF, but each approach should be chosen according to individual patient circumstances. Rate control is the preferred strategy in stable, asymptomatic elderly patients. Current antiarrhythmic agents have either low efficacy or poor safety profile and are likely to be replaced by drugs with novel actions that are more efficacious, atrial specific and less proarrhythmic. The risk of thromboembolism in AF remains substantial. Warfarin significantly reduces thromboembolic episodes, but is vastly underprescribed in elderly patients due to the assumed risk of bleeding. Direct and indirect thrombin inhibitors may become alternative to warfarin therapy. Statins, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are beginning to assume a new role of preventing remodelling and recurrences of AF.

References


(2007) HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace*, 9, 335–379.


