Atrial fibrillation – all change!

Irina Savelieva and John Camm

Irina Savelieva
MD, Lecturer in Cardiology

John Camm
MD FRCP, Professor of Clinical Cardiology

St George's University of London, London

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Atrial fibrillation – a new epidemic

Atrial fibrillation (AF) is said to be an epidemic, affecting 1–1.5% of the population in the developed world.[1] Lifetime risks for development of AF are 1 in 4 for men and women 40 years of age and older.[2] Atrial fibrillation is 12 to 20 times more common in people aged 80–85 years compared with individuals 50–60 years of age.[2,3] The high lifetime risk of AF and increased longevity underscore the important public health burden posed by the condition. The arrhythmia presently costs approximately 1% of the healthcare budget in the UK.[4]

The clinical significance of AF lies in a fivefold increased risk of strokes, which are more severe and are associated with greater disability, and a threefold increased risk of congestive heart failure.[5,6] Atrial fibrillation leads to more hospital admissions than any other arrhythmia and according to recent surveys, the number of AF-related hospitalisations across the world almost tripled in 2000 compared with two decades ago.[7,8] Although AF is classically caused by hypertension, heart failure, myocardial infarction, mitral stenosis, thyrotoxicosis and alcohol, previously unrecognised risk factors, such as obesity, sleep apnoea, and tall stature, have now emerged. Furthermore, genetic predisposition to AF or specific genetically predetermined forms of the arrhythmia (eg in association with short QT syndrome) have been described.

Recently, the challenge of asymptomatic, or silent, AF has been recognised.[9] Paroxysmal and recurrent forms are more likely to be symptomatic, while permanent AF is more often associated with few or no symptoms. The prevalence of sustained silent AF is believed to be 25–30%.

Mechanisms and remodelling

Several theories emerged regarding the mechanism of AF, which can be combined into two groups: the single focus hypothesis (automatic focus, mother wave, fixed rotor, moving rotor) and the multiple sources hypothesis (multiple foci, multiple wavelets, unstable reentry circuits, the combination of a single focus and multiple wavelets).[10] Those who advocate the single focus hypothesis believe that AF is due to a single rapid macroreentry circuit, with wavefronts emanating from the primary driver circuit (rotor) breaking against regions of varying refractoriness, giving rise to irregular global activity characterising the arrhythmia. A single focus fires at a regular, but very rapid rate, which cannot be followed by the rest of the atrial tissue in a 1:1 fashion, thus producing fibrillatory conduction. According to the multiple sources hypothesis, electrical activation in AF proceeds as multiple reentrant wavelets separated by lines of functional conduction block, generating irregular reentrant activity which occurs in a dyssynchronous fashion in various atrial regions (multiple circuit reentry).

It has become obvious over the last few years that atrial electrical properties are altered by sustained AF, such that the atria become more susceptible to the initiation and maintenance of the arrhythmia.[10] Sustained AF in turn induces further electrophysiological and structural alterations of the atrial myocardium, a process known as atrial remodelling. Early in the development of AF, tachycardia-induced calcium overload of atrial myocytes prompts alterations in gene expression leading to down-regulation

Conference programme

- **A new epidemic – atrial fibrillation** Professor Gregory Lip, University of Birmingham and City Hospital, Birmingham
- **Mechanisms of atrial fibrillation and flutter** Professor Maurits Allessie, Cardiovascular Research Institute Maastricht, Maastricht University, The Netherlands
- **Atrial and ventricular remodelling in atrial fibrillation** Professor Clifford Garratt, University of Manchester and Manchester Heart Centre
- **Anti-thromboembolic strategies – warfarin, aspirin, and new wave therapies** Professor Stuart Cobbe, Glasgow Cardiovascular Research Centre, University of Glasgow
- **Rate and/or rhythm control – atrial fibrillation or heart failure** Dr Francis Murgatroyd, King's College Hospital, London
- **Ablation and isolation therapies for the control of atrial fibrillation** Dr Richard Shilling, St Bartholomew's Hospital, London
- **New international guidelines for management of atrial fibrillation** Professor Harry Crijns, University Hospital Maastricht, The Netherlands
- **New national guidelines for management of atrial fibrillation** Professor Gregory Lip, University of Birmingham and City Hospital, Birmingham
- **Therapies just around the corner** Professor John Camm, St George's University of London

of the L-type calcium current. This results in a shortening of the atrial effective refractory period in order to compensate for calcium overload at the expense of a decrease in wavelength, thus promoting multiple wave reentry (electrical remodelling).[11] If AF persists, ultrastructural changes, such as increased cellular volume, sarcomere misalignment, proteolysis and loss of contractile elements, and accumulation of glycogen, may occur, leading to atrial myopathy.[12] Further changes involve remodelling of gap-junctions with reduction in the expression of connexin Cx40 and Cx43. The concept of electrical and structural remodelling is therefore important as it explains why paroxysmal AF tends to become chronic, why longer-lasting AF is harder to treat and why AF recurrence is particularly likely the first few days after electrical cardioversion.

Stroke prevention

About 1 of 6 ischaemic strokes is associated with AF and the majority are due to cardiogenic embolism of left atrial appendage thrombi. The clinical significance of AF-related strokes lies in higher mortality, greater disability, increased costs, and a soaring incidence of recurrent stroke within a year. A number of models have been devised to predict risk of stroke and the likelihood of benefit from therapy with either warfarin or aspirin. Risk factors were identified based on the pooled analysis of 1,593 untreated patients from five primary prevention trials of warfarin (known as Atrial Fibrillation Investigators' risk stratification model) and the results from 2,012 participants from the aspirin arms of the SPAF (Stroke Prevention in Atrial Fibrillation) I-III studies. The $CHADS_2$ scheme is an amalgamation of the individual risk factors: Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, each of which is assigned one point, and prior Stroke or transient ischaemic attack which is given two points (hence, the subscript '2') (Table 1).[13]

A plethora of large randomised clinical trials have convincingly demonstrated the benefits of oral anticoagulation. Warfarin has consistently reduced the risk of ischaemic stroke or systemic embolism by about two thirds compared with no treatment and by 30–40% compared with aspirin in high-risk patients with AF.[14] However, the effect of warfarin is sensitive to changes in diet, liver function, and drug interactions involving the P450 cytochromes and the drug has a very narrow therapeutic window. Consequently, a sub-therapeutic international normalised ratio (INR) of 1.5–1.9 probably reduced the preventive efficacy of warfarin by a factor of 3.6 in AF patients under 75 years and by a factor of 2 in patients over 75 years compared with the recommended INR values. Risk of intracranial haemorrhage with controlled anticoagulation is small (0.3–0.5% per 100 patient-years), but it increases exponentially to 2.7% at INR values between 4 and 4.5 and 9.4% per 100 patient-years when an INR exceeded 4.5.

Table 1. Risk stratification systems for prediction of risk of stroke in atrial fibrillation.

System	Risk factors	Event rate and recommendation
$CHADS_2$	Congestive heart failure = 1 point Hypertension = 1 point Age ≥75 years = 1 point Diabetes = 1 point prior Stroke or TIA = 2 point	Score 0–1: 1.9–2.8% per 100 patient-years Score 2–4: 4.0–5.9% per 100 patient-years Score 5–6: 12.5–18.2% per 100 patient-years
ACC/AHA/ESC guidelines 2006	High-risk factors: previous stroke, TIA or systemic embolism, mitral stenosis; prosthetic heart valve	Any 1 high-risk or >1 moderate-risk factors: warfarin
	Moderate-risk factors: age ≥75 years, hypertension, congestive heart failure, LV ejection fraction ≤35%, diabetes	Any 1 moderate-risk factor: warfarin or aspirin
	Less validated or weaker factors: female gender, age 65–74 years, coronary artery disease, thyrotoxicosis	No risk factors: aspirin 81–325 mg
NICE guidelines 2006	High risk: previous stroke, TIA or systemic embolism, age ≥75 years with hypertension, diabetes or vascular disease (coronary artery disease or peripheral vascular disease), valve disease, congestive heart failure or LV dysfunction	High risk: warfarin
	Moderate risk: age ≥65 years with no high-risk factors; age <75 years with hypertension, diabetes or vascular disease	Moderate risk: warfarin or aspirin
	Low risk: age ≤65 years with no moderate- or high-risk factors	Low risk: aspirin 75–300 mg

ACC/AHA/ESC = American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for the management of patients with atrial fibrillation;[35] $CHADS_2$ Score System;[20] LV = left ventricular; NICE = National Institute for Health and Clinical Excellence;[21] TIA = transient ischaemic attack.

With the advent of more potent antiplatelet agents with better adverse event profiles such as clopidogrel, combined antiplatelet therapy might be more effective than aspirin alone or might be an alternative treatment to oral anticoagulation. However, the ACTIVE (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) failed to show equivalence of combined anti-platelet therapy with aspirin and clopidogrel over dose-adjusted warfarin in 6,706 high-risk AF patients.[15]

Anticoagulant drugs with novel mechanisms of action, such as oral direct thrombin inhibitors and factor Xa inhibitors are currently at different stages of clinical investigation. These agents have theoretical advantages compared to conventional therapy: rapid achievement of therapeutic effect, more dependable pharmacokinetics and lack of interactions, and no need for anticoagulation monitoring. Direct thrombin inhibitors (dabigatran) and oral factor Xa inhibitors (apixabin, rivaroxaban) hold potential for becoming a replacement for warfarin, but further studies are needed to establish their safety and efficacy for the long-term use in AF. Liver involvement may be an inherent safety issue with these agents. For example, the development of ximelagatran, an oral direct thrombin inhibitor, has been terminated because of excess liver enzyme elevation in about 6% of patients and drug-related liver failure and death after the long-term exposure.

Rate or rhythm control

Recently published randomised studies comparing rate and rhythm control strategies have shown that primary rate control is not inferior to rhythm control, and furthermore that rhythm control is more costly and inconvenient than rate control.[16] This has lead to a general movement away from rhythm control in patients who are able to tolerate the arrhythmia when the ventricular rate is adequately controlled. Primary rate control and anticoagulation are acceptable in elderly asymptomatic patients who probably constitute about 60–70% of the AF population (Fig 1). The majority are managed in primary care. The danger of persistent rapid ventricular rates during AF lies in the development of tachycardia-induced cardiomyopathy. The National Institute for Health and Clinical Excellence (NICE) guideline defines adequate rate control in AF as maintenance of the ventricular rate response <90 beats per minute (bpm) at rest and <110 bpm during exercise in elderly, inactive subjects or <200 minus age in younger, physically active individuals.[17] Adequate ventricular rate control at rest does not always translate into effective control during activity, especially with digoxin monotherapy; thus a combination of drugs is often necessary to achieve rate control in AF patients and multiple adjustments of drug type and dosage may be needed to achieve the desired effect.[18]

In many patients electrical or pharmacological cardioversion followed by antiarrhythmic therapy to suppress the arrhythmia is the treatment strategy of choice. The primary rhythm control strategy is appropriate in younger individuals, ie less than 60–65 years, patients who are highly symptomatic, individuals with recent onset AF, and patients with AF and associated congestive heart failure. Analysis of subgroups in the rate versus rhythm trials showed that those who were in sinus rhythm and those who used anticoagulants survived better while those who were treated with antiarrhythmic drugs had a higher mortality.[19] Unfortunately currently available antiarrhythmic drugs, amiodarone, sotalol, propafenone and flecainide, are only moderately effective at initially reducing the incidence of paroxysms or preventing persistent AF, and patients may later become unresponsive or develop side effects.

Non-pharmacological treatment

Dissatisfaction with the current rhythm-control drugs and the discovery of specific mechanisms of AF, such as very fast pulmonary vein tachycardia, led to the rapid development of non-pharmacological treatment alternatives, including various catheter-based percutaneous and surgical techniques. Atrioventricular node ablation followed by permanent pacemaker implantation known as the 'ablate and pace' strategy is used as a last resort to control ventricular rates in permanent, drug-resistant AF. It is a palliative procedure which renders the patient pacemaker-dependent and is reserved for older individuals in whom there is no treatment alternative. Paroxysmal forms of AF

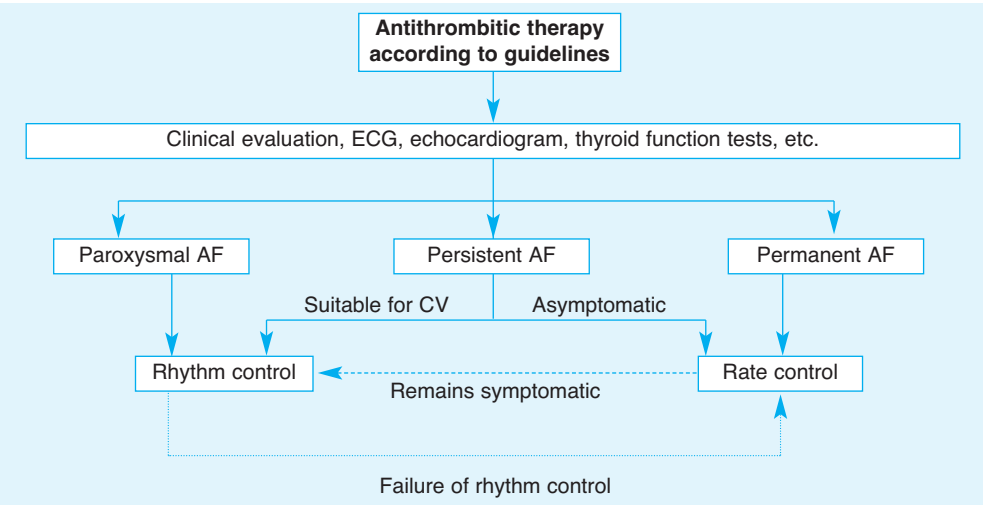

Fig 1. Treatment strategy decision tree. AF = atrial fibrillation; CV = cardioversion; ECG = electrocardiogram.

can be treated with pulmonary vein isolation to prevent the induction of AF by rapid repetitive pulmonary vein ectopic activity emanating from 'sleeves' of the atrial myocardium inside the pulmonary veins. The procedure has a success rate approaching 75–85% compared with 5–35% on antiarrhythmic drug therapy in patients without clinically significant structural heart disease. There is evidence from the non-randomised cohort study that elimination of AF with pulmonary vein isolation is associated with lower mortality.[20]

The eventual impact of pulmonary vein isolation is not yet known but is likely to be successfully used in younger patients with paroxysmal AF and near normal hearts (possibly 10% of the population).

The surgical maze procedure is presently limited to patients undergoing other heart surgery, eg mitral valve repair or replacement (<1% of patients with AF). As these operations become minimally invasive and highly effective they are likely to be more widely used.[21]

National Institute for Health and Clinical Excellence guideline

The NICE guideline on AF, published in 2006, represents a pragmatic and applicable evidence-based approach to AF management and is focused on primary and non-specialist secondary care.[17] When physicians identify patients with an irregular pulse they should record an electrocardiogram (ECG) (preferably a 12-lead ECG) in order to confirm or refute the possible diagnosis of AF. The ECG recording may also give information about underlying cardiovascular disease (ischaemia, infarction, hypertension, etc). Once the diagnosis of AF is made, the risk of thromboembolism should be systematically assessed using predominantly a modified $CHADS_2$ scoring system. Although it is acknowledged that echocardiography will be needed for most patients who present with AF in order to evaluate the causes and/or the consequences of the arrhythmia (hypertrophy, dilation, thrombus, spontaneous echo contrast, ischaemia/infarction, etc), obtaining the investigation should not usually delay the implementation of anticoagulant therapy when already clearly identified as necessary because of associated cardiovascular disease.

Identification of clinical subgroups of patients help to define an objective approach to management, based on the notion that the rate control strategy is not necessarily inferior to rate control. The NICE guidelines review the rate versus rhythm control trials and conclude that for many patients a simple rhythm control (± anticoagulation) strategy is all that is needed. It is important to understand, however, that younger patients, especially when symptomatic from AF or suffering from heart failure, may benefit much more from rhythm rather than rate control. The NICE guideline proposes a stepwise approach to rhythm control management, balancing the efficacy and side effects of antiarrhythmic drugs with underlying heart disease and comorbidities. Rhythm control rests primarily on the use of beta blockers but if these drugs fail to suppress the arrhythmia, specific antiarrhythmic agents may be used depending on the presence (amiodarone) or absence (sotalol, flecainide or propafenone) of significant underlying heart disease such as heart failure, hypertension with hypertrophy, ischaemic heart disease in the presence of recurrent ischaemia or previous infarction). Sotalol and amiodarone are thought equally effective in patients with moderate ischaemic heart disease. A 'pill-in-the-pocket' approach using oral flecainide or propafenone can be offered to patients with little structural heart disease, low risk of cardiogenic thromboembolism and infrequent symptomatic paroxysms of AF.[22] Rate control, traditionally achieved with digoxin monotherapy, should be treated first with either a beta blocker or non-dihydropyridine calcium antagonist. Digoxin monotherapy is not appropriate except in inactive patients, but can often be usefully added to background beta blockade or non-dihydropyridine calcium antagonist treatment in order to achieve better rate control at rest.

The NICE guidelines acknowledge that referral to a cardiologist or arrhythmia specialist (clinical electrophysiologist) may be necessary in highly symptomatic patients who are refractory to the basic therapy for AF. In such cases the specialist may resort to the use of non-pharmacological therapies which may substantially eliminate the arrhythmia or even 'cure' the condition. Non-pharmacological approaches are useful when adequate drug therapy is ineffective or intolerable.

American College of Cardiology/American Heart Association/European Society of Cardiology guidelines

While the NICE guideline deals mainly with primary and non-specialist secondary care for AF, the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines, published in 2006, are designed to assist a wide range of healthcare providers in clinical decision making by describing an array of evidence-based approaches to the diagnosis, management, and prevention of AF, including AF associated with specific diseases and conditions. The 2006 ACC/AHA/ESC guidelines include a detailed, safety-based algorithm for selection of antiarrhythmic drug therapy.[23] When rhythm control is contemplated, underlying structural heart disease is essential for the selection of an antiarrhythmic drug. Class IC antiarrhythmic agents, flecainide or propafenone, or sotalol may be the drug of choice in lone AF or AF associated with hypertension without significant left ventricular hypertrophy, sotalol or dofetilide (available in North America) in patients with coronary disease, amiodarone or dofetilide in the presence of left ventricular dysfunction and overt congestive heart failure or if class IC agents are ineffective. Of note, class IA antiarrhythmic drugs such as quinidine, procainamide, and disopyramide, are no longer recommended by guidelines, although some can be used empirically in patients with certain forms of AF (eg anticholinergic activity of disopyramide may be useful in vagally-mediated AF). When treatment with a single antiarrhythmic drug fails, combinations (eg a beta blocker, sotalol, or amiodarone with a class IC agent) may be tried. An important difference of the new guidelines is that ablation-based techniques have been raised to the second choice in patients who failed at

least one antiarrhythmic drug. The updated ACC/AHA/ESC guideline reconsidered the previous risk stratification for thromboembolic risk and downgraded several risk factors rendering them 'less validated or weaker' on the grounds of lack of evidence. These include variables such as female gender, coronary artery disease, age (65 to 74 years), and thyrotoxicosis. Advanced age (>75 years), hypertension, heart failure, and diabetes mellitus are considered moderate risk factors, whereas only three variables, mitral stenosis, prosthetic heart valve, and prior cerebrovascular accident, identify patients at high risk according to the new guidelines.

Future directions

An attractive prospect for AF therapy is the introduction of agents with selective affinity to ion channels specifically involved in atrial repolarisation, so-called atrial repolarisation delaying agents (ARDAs). The ultra-rapid component of the delayed potassium rectifier current (I_{Kur}) is expressed in human atrial tissue but not in human ventricular myocardium. Vernakalant (RSD 1235, Cardiome) is in the most advanced phase of development and investigation. The greatest efficacy (about 70%) was reported for recent onset AF of less than 72 hours. The drug was ineffective for conversion of AF of more than seven days and atrial flutter. Other possibilities include modified structural analogues of traditional antiarrhythmic drugs with additional novel mechanisms of action and less complex metabolic profiles that may improve their efficacy and safety (for example, propafenone slow release, dronedarone, and 'soft' amiodarone).[24] Dronedarone (sanofi-aventis) is an investigational agent with multiple electrophysiological effects, in which it is similar to amiodarone, but it is devoid of iodine and is believed to have a better side-effect profile.[25]

There is accumulating evidence in support of the antiarrhythmic effects of traditional non-antiarrhythmic drugs. Agents targeting inflammation, oxidative injury, atrial myocyte metabolism, extra cellular matrix remodelling, and fibrosis have theoretical advantages as potential novel therapeutic strategies. Treatments with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), statins, and omega-3 fatty acids all seem promising, over and above any effect related to the treatment of underlying heart disease.[26,27]

A battery of novel mechanical approaches for the prevention of cardioembolic stroke has recently been evaluated, including various models of percutaneous left atrial appendage transcatheter occluders which block the connection between the left atrium and the left atrial appendage, minimally invasive surgical isolation of the left atrial appendage, and implantation of the carotid filtering devices which divert large emboli from the internal to the external carotid artery, preventing the embolic material from reaching the intracranial circulation.

In any event, the application of such expensive and technologically demanding procedures to the millions of AF sufferers is unlikely. A pharmacological, and preferably a preventative, strategy is needed to cope with an epidemic of the size presented by AF.

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