Seminar

Atrial fibrillation: strategies to control, combat, and cure

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Atrial fibrillation is the commonest clinical arrhythmia, is increasing in incidence and prevalence, and is associated with substantial morbidity and mortality. The arrhythmia may be paroxysmal (self-limiting), persistent (amenable to cardioversion), or permanent. Especially in its paroxysmal form, atrial fibrillation may be initiated by rapidly firing foci, generally located in the proximal pulmonary veins. Sustained atrial fibrillation is maintained by an atrial tissue substrate capable of accommodating many meandering wavelets. With continuing arrhythmia, the electrophysiological properties of the atria change and further facilitate continuing fibrillation. Treatment is aimed at prevention of thromboembolic complications, restoration and maintenance of sinus rhythm, and control of ventricular rate during atrial fibrillation. With greater understanding of the arrhythmia mechanisms, it is becoming possible to offer targeted curative treatments to more and more patients.

Few challenges have been more resistant to advances in clinical medicine than atrial fibrillation; diagnosis of this arrhythmia is made with a clinical tool that has remained largely unchanged since the 19th century, the electrocardiogram (ECG). These two facts might not, however, be entirely unrelated. The ECG, although useful in clinical practice, is a fairly blunt tool, refinement of which has added little to the understanding of mechanisms of atrial fibrillation. As a result, various treatments have been developed, some of which are empirical, and many of which fail to address the underlying pathophysiology, which has remained largely unknown. However, in the past few years increased recognition and understanding of two major ideas have given rise to much enthusiasm and the prospect of more effective treatments. First, an increasingly recognised and growing number of patients have atrial fibrillation that is initiated, and sometimes maintained, by an ectopic focus of repetitive atrial activity, usually arising from a pulmonary vein.[1] Second, fibrillation of the atrial myocardium causes changes in cellular electrophysiology that, at least in animals, further increase the tendency to fibrillation,[2] and that are reversed after a period of sinus rhythm.[3] The first notion relates mainly to the triggers for initiation of the arrhythmia, and the second to the myocardial substrate predisposing to and maintaining the arrhythmia.

In parallel with these evolving ideas, developments in clinical cardiac electrophysiology in the past few years have allowed cardiologists to cure almost all regular tachycardias with the percutaneous technique of radiofrequency ablation. Electrode catheters are used to map the arrhythmia and to deliver radiofrequency energy, causing localised tissue necrosis at sites essential for the arrhythmia, with high rates of complete cure. These therapeutic successes in management of regular arrhythmias have driven efforts to improve understanding of the mechanisms of the most common and resistant cardiac arrhythmia, atrial fibrillation, and to develop better treatment strategies than previously used. These efforts have resulted in further clarification of almost all aspects of this arrhythmia, and the extent to which these ideas have shaped our approach to atrial fibrillation in the clinic forms the major focus of this seminar. This seminar should be read in conjunction with that of Narayan and colleagues,[4] which covers clinical matters not covered here, and with the guidelines for management of patients with atrial fibrillation.[5]

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Epidemiology

Atrial fibrillation is the commonest sustained cardiac arrhythmia. Prevalence of this disorder increases with age, rising above 5% in people older than 65.[6] The disorder is also becoming more prevalent with time, even after adjustment for age and structural heart disease.[7] Hypertensive, valvular, ischaemic, and other types of structural heart disease underlie most cases of chronic atrial fibrillation. From long-term follow-up data of the Framingham study, independent risk factors for atrial fibrillation include male sex, hypertension, diabetes, heart failure, and valvular heart disease. Myocardial infarction is an independent risk factor for development of atrial fibrillation in men only, increasing the likelihood of this disorder by 40% in this group. Echocardiographic variables, including left atrial dilatation, left ventricular hypertrophy, and impaired systolic function are also strongly associated with development of atrial fibrillation.[7] Because of its high prevalence, hypertension is responsible for more cases of atrial fibrillation in the population (14%) than any other risk factor. Data from the Framingham study[8] suggest that lone atrial fibrillation (atrial fibrillation in a heart that seems to be otherwise structurally and functionally normal) accounts for about 15% of all cases of this disorder in the community, with a peak prevalence in patients aged 60–79 years. However, most epidemiological data on atrial fibrillation are derived from mainly white populations in more-developed countries, and little is known about potentially different epidemiology in other groups and regions.[9]

Search strategy and selection criteria

We did a comprehensive review of work published from January, 1966, to November, 2001, that was relevant to atrial fibrillation from PubMed/Medline, EMBASE, and Cochrane Library databases. A few articles that were published before 1966, but addressed major contributions to this subject were also included. We selected studies that contributed most to the knowledge of the epidemiology and pathogenesis of the disease. In the case of studies on treatment of atrial fibrillation, we selected large randomised controlled studies, whenever such data were available. The key words used were: atrial fibrillation.

Atrial fibrillation increases risk of stroke six-fold (much more in patients with rheumatic heart disease), and becomes increasingly important as a risk factor for stroke with increasing age, with an attributable risk that rises from 1·5% for patients in their 50s to 23·5% for those in their 80s. It is associated with a doubling of mortality in both sexes, which remains above 1·5-fold after adjustment for comorbidity.[7] Increased mortality is mainly due to cerebrovascular events, progressive ventricular dysfunction, and increased coronary mortality. The relative contribution of these factors varies depending on the population studied.[10–12] The 5–20% of patients with myocardial infarction who develop atrial fibrillation have increased mortality, an effect only partly attributable to ventricular dysfunction in this group.[13]

Classification

Atrial fibrillation is mostly classified according to its temporal pattern (panel 1). A patient presenting with this disorder could have a first detected episode of atrial fibrillation, or recurrent arrhythmia if they have had previous documented episodes. Episodes are paroxysmal if they terminate spontaneously, or persistent if they require electrical or pharmacological cardioversion. Atrial fibrillation that cannot be successfully stopped by cardioversion and long-standing (>1 year) atrial fibrillation, in which cardioversion has not been attempted, is termed permanent.[5]

Paroxysmal atrial fibrillation accounts for 35–66% of all cases of atrial fibrillation, with prevalence peaking at age 50–69 years.[14–16] The prevalence is probably greatly underestimated, since data from serial Holter monitoring suggest that many atrial fibrillation episodes are symptomless.[17] The probability that lone atrial fibrillation will progress from paroxysmal to permanent is about 20%, and varies by population and duration of follow-up.[15] The epidemiology of the subgroup in whom atrial fibrillation is initiated by ectopic electrical activity arising from a focal source is less well described, but the arrhythmia can affect patients with hearts that are structurally normal and have no other abnormalities, and patients with structural heart disease; the disease is most common in patients in their 50s and 60s, and three times more common in men than women.[1]

Pathophysiology

Electrophysiological effects

Several experimental and human mapping studies done over the past 30 years have shown that atrial fibrillation is characterised by multiple wavelets of excitation that propagate around the atrial myocardium, and that perpetuation of the arrhythmia is the result of an abnormal atrial tissue substrate.[18] Atrial fibrillation in general results from a complex interaction between initiating triggers and development of this abnormal tissue substrate capable of maintaining the arrhythmia. Although many patients with atrial fibrillation have structural heart disease, the cause of this disorder in patients whose hearts seem to be healthy is less well understood. Although there seems to be a large overlap, younger patients with healthy hearts and paroxysmal atrial fibrillation generally have a trigger-predominant mechanism, whereas patients with structural heart disease and permanent atrial fibrillation have a substrate-predominant mechanism.[19]

Panel 1: Nomenclature for atrial fibrillation

Acute	an episode of atrial fibrillation, usually within 48 h of its onset
Paroxysmal	intermittent, recurrent, and self-terminating
Persistent	will not self-terminate, but can be effectively cardioverted to sinus rhythm
Permanent	atrial fibrillation that cannot be terminated by cardioversion, that can be terminated only for brief intervals, or that lasts longer than 1 year without cardioversion having been attempted
Chronic	implies continuing atrial fibrillation and does not address the important clinical distinction between persistent and permanent atrial fibrillation
Focal	atrial fibrillation is initiated (focally initiated atrial fibrillation), or sometimes maintained (true focal atrial fibrillation) by arrhythmogenic foci, often in pulmonary veins. It could be paroxysmal or persistent

Tissue substrate capable of maintaining atrial fibrillation

The notion of re-entrant wavefronts causing arrhythmias was first suggested by Mines,[20] and then promoted by Lewis between 1904 and 1924.[21] By the early 1980s, there were several proposed mechanisms for atrial fibrillation, which remained largely unproven in vivo. These included: a central wave that propagates incessantly and regularly through a fixed circular path (macro-reentry) and spawns daughter wavelets at irregular intervals; many unsynchronised focal sources; and many wavelets that meander randomly,[22] the number of which determines the stability and likelihood of termination of atrial fibrillation.[23]

The advent of multielectrode mapping systems allowed activation patterns to be studied in human beings during cardiac surgery and with percutaneous techniques. Although the patterns of activation vary both between patients and between the two atria of individual patients, with one atrium sometimes showing a much greater degree of organisation than the other, and with occasional macro-reentrant circuits or apparent focal activation in one atrium, the dominant mechanism incorporates multiple meandering wavelets, both in acutely-induced and chronic atrial fibrillation.[24–29]

Remodelling in atrial fibrillation

Shortening of the refractory period (the unexcitable period after activation) is a fundamental electrophysiological change of the atrial myocardium that helps to perpetuate the arrhythmia, by allowing more wavelets in the atrial mass. Both paroxysmal[30] and persistent atrial fibrillation are associated with shortening of the refractory period, but this change could become more permanent in long-term atrial fibrillation. Results of studies of adaptation of the atria to the fibrillatory state have shown that progressive changes in atrial electrophysiology, such as substantial shortening of refractory periods, could be caused by fibrillation itself, giving rise to the adage that "atrial fibrillation begets atrial fibrillation". In animal studies that simulate a permanent fibrillatory state, changes in ion channel function,[31] and shortening of refractory periods start within minutes, and after 24 h of atrial fibrillation the atrium has been sufficiently remodelled that the stability of atrial fibrillation increases, and when it occurs, it eventually becomes persistent. Even after 2 weeks of persistent atrial fibrillation, however, restoration of sinus rhythm results in a rapid reversal of the electrophysiological remodelling in animals.[2]

Electrical remodelling, and its reversal, might also take place in human beings. Patients with paroxysmal atrial fibrillation have increased dispersion of refractoriness between different parts of the atria, and shorter refractory periods than controls.[30] Right-atrial refractory periods in human beings are short immediately after cardioversion of persistent atrial fibrillation, and seem to lengthen again

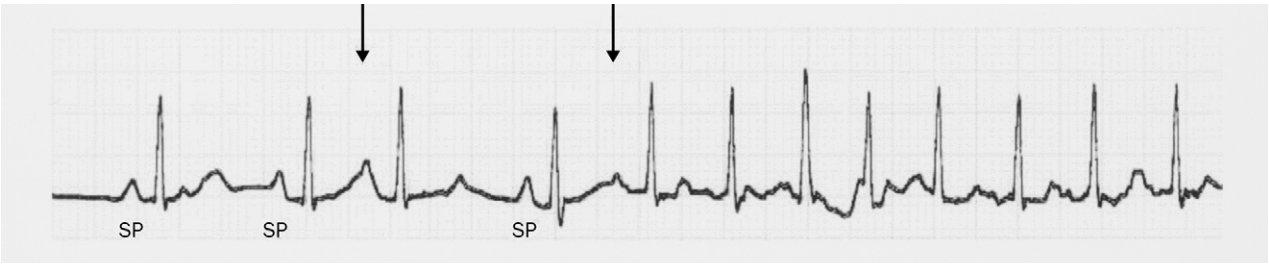

Figure 1: **Initiation of atrial fibrillation by ectopic beats**
The first atrial ectopic beat (first arrow), which is superimposed on the T wave, follows two normal sinus rhythm P waves (SP), and closely follows the previous sinus beat, does not initiate atrial fibrillation. However, atrial fibrillation is initiated in the subsequent ectopy (second arrow).

within 4 weeks; [32] patients are at high risk of recurrence in the first few days after cardioversion from atrial fibrillation.[33] Moreover, the duration of the antecedent atrial fibrillation episode in human beings is a potent predictor of sinus rhythm maintenance after cardioversion.[34] Patients with recurrent atrial fibrillation could develop increasing problems with time and many might progress to permanent atrial fibrillation.[8,35,36] Although reverse remodelling after restoration of sinus rhythm does take place in human beings who have established atrial fibrillation,[3,37] results of some studies have suggested that this might no longer be possible after very long periods of atrial fibrillation. Indeed, the ability to cardiovert to sustained sinus rhythm is greatly reduced in patients who have been in persistent atrial fibrillation for longer than 12 months.[38]

In animals, these changes in cellular electrophysiology arise within hours to days, but atrial fibrillation can take weeks to become persistent, suggesting that other factors are probably involved in this process. Although a second factor in the adaptation of the atria to fibrillation has not been conclusively shown, histological changes have been identified in animals, that are similar to those seen in patients with longstanding atrial fibrillation.[39]

Focal initiators of atrial fibrillation

Ectopic atrial activation, usually emerging from one or more foci often located in the muscular sleeves of the proximal pulmonary veins as single beats or repetitive bursts of activity, is an important contributor to initiation of atrial fibrillation in human beings (figure 1).[1] Less frequently, other sites, including the proximal superior vena cava,[40] the ligament of Marshall,[41] and other parts of the right and left atria give rise to ectopy that could initiate atrial fibrillation. Although this focal atrial fibrillation is usually paroxysmal, at least in its early stages, and can affect patients with apparently structurally normal atria,[42,43] a mechanism of focal initiation may also underlie many cases of persistent atrial fibrillation, with or without structural heart disease.[44]

Muscular sleeves extending into the proximal pulmonary veins (figure 2) are found in the hearts of all human beings. The upper veins have more prominent muscular sleeves and are more likely to be the source of atrial fibrillation induced by ectopy than the lower veins, but the extent of these sleeves does not differ between individuals with or without atrial fibrillation.[43] The mechanism by which abnormal activity is produced by these pulmonary venous and other initiating atrial ectopic foci, and the exact mechanism by which this localised focal ectopic activity results in the generalised fibrillatory activity throughout the atria, remain largely unknown. Proposed mechanisms for generation of abnormal focus activity include increased automaticity and triggered activity (abnormal electrophysiology generating extra depolarisations of cells), or very small reentrant circuits between small numbers of cells.[45]

Genetics of atrial fibrillation

Although the rare familial occurrence of atrial fibrillation has been recognised for some time,[46] the location of the gene responsible for this disorder has only recently been identified in a family in whom the arrhythmia segregated as an autosomal dominant trait (10q22–q24).[47] Brugada and colleagues[48] have since identified many more families who have atrial fibrillation, and found that the locus on chromosome 10 did not contain the gene responsible for atrial fibrillation in all families, suggesting that familial atrial fibrillation is a heterogeneous disease caused by more than one gene.

Haemodynamic and prothrombotic effects

Atrial fibrillation has many adverse haemodynamic effects that relate not only to loss of atrial contraction and thus atrioventricular synchrony, but also to the accompanying rapidity and irregularity of ventricular contraction.[49] These effects are especially relevant to patients with underlying systolic ventricular dysfunction, and those with diastolic dysfunction or mitral stenosis in whom cardiac function depends more on a long diastole and active ventricular filling than a healthy heart.

The loss of atrial contraction that accompanies atrial fibrillation leads to stasis. Stasis is most marked in the left atrial appendage, the most common site for thombus formation in these patients. Stasis is accompanied by hypercoagulability, as shown by increased concentrations of fibrinogen and fibrin D-dimer and endothelial dysfunction, evidenced by increased concentrations of von Willebrand factor. All three components of this triad probably contribute to development of the prothrombotic state that accompanies atrial fibrillation.[50]

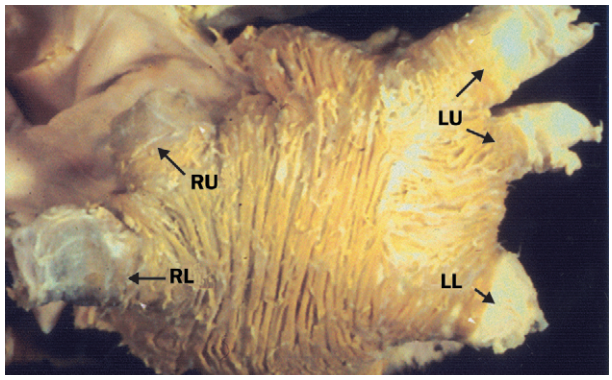

Figure 2: **Subendocardial myoarchitecture of the left atrium and proximal pulmonary veins**
The left atrium and pulmonary veins have been everted to show the subendocardial fibre orientation. Note that myocardial fibres extend into the pulmonary veins past the veno-atrial junctions (arrows). LU=left upper pulmonary vein. LL=left lower pulmonary vein. RU=right upper pulmonary vein. RL=right lower pulmonary vein. Reproduced with permission from Siew Yen Ho and Damian Sanchez-Quintana.

Panel 2: **Baseline assessment of patients with suspected atrial fibrillation**

History and examination
Identify reversible causes and risk factors, including structural heart disease, hypertension, thyrotoxicosis, and excessive consumption of alcohol
Identify the presence or absence and severity of symptoms, and how they might interfere with the patient's lifestyle
Define arrhythmia duration and clinical picture: recent onset paroxysmal, chronic

Electrocardiogram
Evidence of hypertensive or ischaemic heart disease, or cardiomyopathy
In sinus rhythm:
- Amplitude and duration of P waves
- Evidence of frequent supraventricular ectopic activity

In atrial fibrillation:
- Confirm diagnosis
- Determine whether there are periods of organised atrial activity, atrial flutter, or atrial tachycardia

Holter monitoring
Used for patients who are in sinus rhythm at presentation to:
- Document the arrhythmia
- Examine its association with ectopic activity or episodes of bradycardia

Used for some patients who are in atrial fibrillation at presentation to assess control of ventricular rate

Electrolytes and thyroid function tests

Echocardiogram
Left atrial size
Mitral valve function
Pulmonary vein size (if visible)
Left ventricular dimensions and function

Effect on quality of life

Although atrial fibrillation can be symptomless, up to two-thirds of patients report that the arrhythmia is disruptive to their lives.[51] Cerebrovascular complications are a further important cause of functional limitation in patients with atrial fibrillation.

Diagnosis

Diagnosis of atrial fibrillation is based on history and clinical examination and confirmed with a 12-lead ECG. However, patients with atrial fibrillation do not always have symptoms. In the Cardiovascular Health Study,[52] 12% of new cases of atrial fibrillation were diagnosed on the basis of yearly ECG screening alone, and thus presumably had no symptoms. In recurrent atrial fibrillation, patients may have a history suggestive of a paroxysmal tachycardia, which might be perceived as episodic irregular palpitations, breathlessness, chest pain, or dizziness. Holter monitoring is often useful, not only because many paroxysmal episodes could also be symptomless,[17] but also to document an association between atrial ectopy or runs of focal atrial tachycardia and atrial fibrillation initiation. In patients with infrequent, but symptomatic episodes, the arrhythmia is best seen with patient-activated event recorders. For patients who have had a modern pacemaker implanted, the diagnostic and memory functions of these pacemakers can allow accurate and automatic detection of atrial fibrillation, with retrieval of stored electrocardiograms during arrhythmic episodes.[53] Panel 2 shows the recommended minimum baseline assessment for patients presenting with atrial fibrillation.

Panel 3: **Principles of atrial fibrillation management**

(refer to text and figure 3)
Restoration of sinus rhythm
Electrical cardioversion
- External
- Internal

Pharmacological cardioversion

Maintenance of sinus rhythm
In patients with recurrent, or after cardioversion of persistent atrial fibrillation
- No treatment

Drug treatment
Permanent pacing
Radiofrequency ablation
- Focal
- Linear

Surgery

Ventricular rate control
Drug treatment
- Calcium-channel blockers
- β-adrenoceptor antagonists
- Digoxin

Modification or ablation of the atrioventricular node, and implantation of a permanent pacemaker

Reduction of thromboembolic risk
Warfarin or aspirin

Treatment

Panel 3 shows the principles of management of atrial fibrillation, with an algorithm for management of atrial fibrillation in figure 3, which should be read together with published guidelines.[5]

Restoration of sinus rhythm

In patients with atrial fibrillation, restoration and maintenance of sinus rhythm could improve symptoms, correct atrial remodelling associated with the arrhythmia, reduce risk of thromboembolism, and remove the need for indefinite anticoagulation. Irrespective of whether underlying heart disease is present, restoration of sinus rhythm is associated with improvements in exercise capacity and peak oxygen consumption.[54]

With increasing duration of antecedent atrial fibrillation, the probability of successful cardioversion decreases irrespective of the technique used, and recurrence of arrhythmia becomes more and more likely. Early restoration of sinus rhythm is thus an important goal whenever it can be safely achieved.

Patients who have been in atrial fibrillation without anticoagulation for more than 48 h need to be adequately anticoagulated (international normalised ratio 2·0–3·0) for at least 3 weeks before cardioversion (either pharmacological or electrical), can be safely attempted.[55] An alternative approach for patients who have been in atrial fibrillation for more than 48 h is administration of heparin, followed by transoesophageal echocardiography, which has a high sensitivity for detecting atrial thrombi. Although occasional cases of embolism in the absence of visible thrombus have been reported, this approach is becoming more common.[56] Since atrial fibrillation causes mechanical dysfunction of the atria that could recover slowly after cardioversion, anticoagulation should be maintained for at least 1 month after cardioversion, even if transoesophageal echocardiography has shown no thrombus just before cardioversion.[55,56]

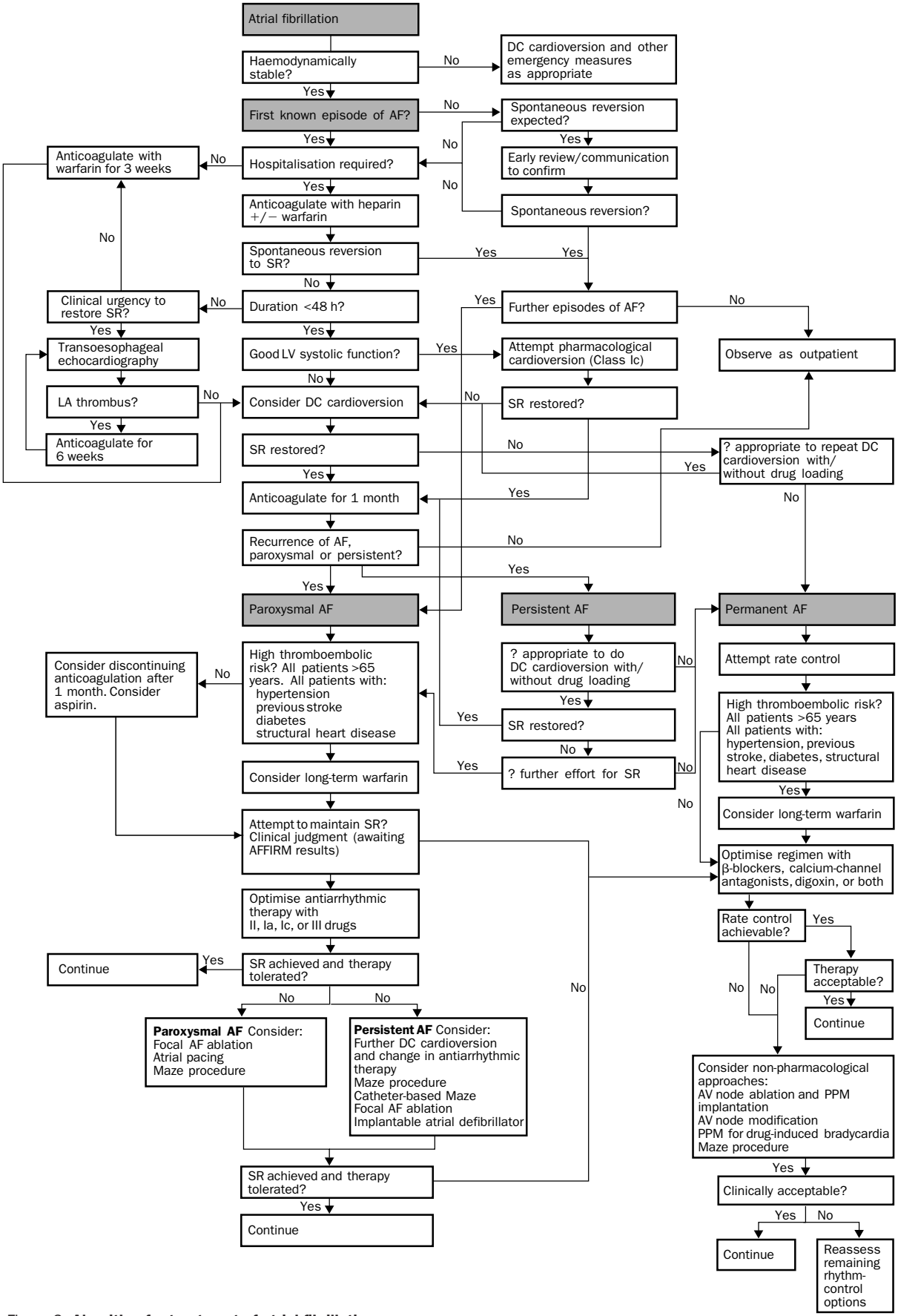

Figure 3: **Algorithm for treatment of atrial fibrillation**
AF= atrial fibrillation. DC=direct current. SR=sinus rhythm. LV=left ventricular LA=left atrial. PPM=permanent pacemaker. AFFIRM=Atrial Fibrillation Follow-up Investigation of Rhythm Management. AV=atrioventricular.

Pharmacological cardioversion

Pharmacological cardioversion is often effective for treatment of recent onset atrial fibrillation, but efficacy is greatly reduced if atrial fibrillation has persisted for longer than 48 h. Thus, for patients who have been in atrial fibrillation for less than 48 h, pharmacological cardioversion is a reasonable approach. Although prolonged anticoagulation before cardioversion is not needed for patients presenting within 48 h of onset of atrial fibrillation, administration of intravenous heparin, initiated at presentation, has been recommended, and could allow more flexibility in subsequent management of the arrhythmia than was previously possible.[57] For example, if pharmacological cardioversion proves ineffective, electrical cardioversion could be done after the 48-h window in patients who have received heparin from the time of presentation. However, this approach of early cardioversion can only be safely adopted if there is a clear history of symptom onset within 48 h, irrespective of whether or not intravenous heparin is given.

Results of many small studies have shown that intravenous flecainide is effective in restoring the sinus rhythm during acute atrial fibrillation. In these studies,[58] the overall efficacy of flecainide was 72–95%, with the greatest success rates in patients who received treatment within 24 h of arrhythmia onset. In a randomised comparison[59] of intravenous flecainide, propafenone, and amiodarone for treatment of recent onset atrial fibrillation, a significant difference in efficacy was noted between the three drugs, with 90%, 72%, and 64% of patients in the three groups, respectively, reverting to sinus rhythm within 12 h of drug administration.

Although pharmacological cardioversion is much less likely to be effective when atrial fibrillation has been present for longer than 48 h, administration of high-dose dofetilide to patients who have had atrial fibrillation for longer than 2 weeks restores sinus rhythm after 3 days in 22–42% of patients.[60] However, because of the risk of provoking serious ventricular arrhythmias, patients should be treated and monitored in hospital.[61] The most effective drug for restoration of sinus rhythm in more persistent atrial fibrillation seems to be amiodarone, with one small study[62] reporting success in 44% and 68% of patients at 2 days and 9 months, respectively.

Electrical cardioversion

For patients with persistent atrial fibrillation, synchronised external cardioversion under general anaesthesia is safe and effective, with success rates of 65–90%. At present, R-wave synchronised shocks, starting at 200 J, and increasing if necessary to 360 J are recommended,[55] although the cumulative energy needed can be lowered with an initial 360 J shock.[63] Shock energy and waveform, electrode size and position (anteroapical *vs* anteroposterior), and transthoracic impedance can affect the likelihood of successful cardioversion.

If electrical cardioversion has not been successful, treatment with class-III agents including sotalol, amiodarone, and ibutilide can help to reduce the threshold for atrial defibrillation, and facilitate electrical cardioversion.[64–66] However, ibutilide in particular can cause serious proarrhythmia, especially in patients with poor ventricular function, and treatment should therefore be initiated and monitored in hospital. Treatment with class-Ic agents also facilitates electrical cardioversion, although the effect on the atrial defibrillation threshold is less clear.[67,68]

Internal cardioversion with percutaneous electrode catheters for delivery of synchronised low-energy shocks between the right atrium and coronary sinus or left pulmonary artery under sedation can restore sinus rhythm in up to 90% of patients in whom external cardioversion has failed.[69]

This same arrangement of internal electrodes (right atrium and coronary sinus) has been developed for use with implantable atrial defibrillators. These devices can be implanted much like permanent pacemakers, and allow early cardioversion of recurrent persistent atrial fibrillation. Although the device can be activated by the patient, the low energy (3–5 J) shocks are still painful and, in practice, most treatments are delivered with sedation under medical supervision. Although early cardioversion with the implantable atrial defibrillator can keep atrial remodelling that has been induced by atrial fibrillation to a minimum and allow progressive reduction of the burden of atrial fibrillation,[70] clinical experience with the device has generally been disappointing, and it is not in widespread clinical use.

Maintenance of sinus rhythm

Digoxin has no effect on the rate of conversion of atrial fibrillation of recent onset to sinus rhythm, or in preventing recurrence.[71–73] Pure β-adrenoceptor antagonists have a small beneficial effect in maintainance of sinus rhythm in patients who have been cardioverted from atrial fibrillation.[74] Two studies[75,76] have shown no difference, either in reduction of atrial fibrillation burden in patients with paroxysmal atrial fibrillation, or in the probability of atrial fibrillation relapse after cardioversion, between sotalol and pure β-1 adrenoceptor antagonists. However, more proarrhythmic events were recorded with sotalol than with β-1 adrenoceptor antagonists.[76]

In the largest randomised series[77] comparing sotalol with propafenone and placebo, sotalol was more effective than either propafenone or placebo at controlling paroxysms of atrial fibrillation. Flecainide[78] and propafenone[79] are more effective than placebo at suppressing symptomatic paroxysms of atrial fibrillation.[80] Flecainide and propafenone are equally potent at suppressing atrial fibrillation paroxysms, and neither is associated with significant proarrhythmia in the absence of structural heart disease.[81,82] Both agents are more effective than quinidine[83] and are tolerated better than either quinidine or disopyramide.[84,85]

Investigators of four studies[86–88] have looked at the efficacy of amiodarone in maintenance of sinus rhythm in patients with paroxysmal or chronic atrial fibrillation refractory to other drugs. In these studies, the probability of suppression of atrial fibrillation in these patients at 1–3 years after onset was 50–80%. Amiodarone is also much better than either sotalol or propafenone in maintainance of sinus rhythm in patients with a history of atrial fibrillation.[89]

Ultimately, the choice of drug for maintenance of sinus rhythm will vary between patients, depending on cardiac function, comorbidity, and contraindications. β-adrenoceptor antagonists are preferable in patients with relatively healthy hearts, with class-Ic agents as an alternative, and amiodarone reserved for patients who are unresponsive to other drugs, or those with poor cardiac function.

Pacing

Atrial pacing can suppress paroxysms of atrial fibrillation by preventing bradycardic episodes, suppressing ectopic beats arising from the pulmonary veins or atria, or reducing the interatrial conduction delay and dispersion of refractoriness.[90–92] Although standard DDD pacing with mode switching seems to be efficacious,[93] pacing algorithms that result in near-continuous atrial pacing can be especially successful in suppression of atrial fibrillation paroxysms.[94–96] Multisite (dual-site right atrial or biatrial [right atrium and

coronary sinus]) pacing, or pacing at the interatrial septum,[97] with a minimum rate of 80–90 beats per min, could also suppress the arrhythmia,[96,98] although results of studies[93] in which lower minimum pacing rates were used (70 beats per min) have not confirmed this benefit. Temporary biatrial pacing is also more effective than single-site atrial pacing in prevention of atrial fibrillation after coronary artery surgery.[99]

Radiofrequency ablation of foci initiating atrial fibrillation

The pulmonary veins are now known to be the main source of paroxysmal left atrial tachycardias[100] and focally initiated atrial fibrillation.[1,44] Percutaneous catheters can be used to identify the location of arrhythmogenic foci within pulmonary veins. Mapping can be done during sinus rhythm with ectopy or during atrial tachycardia, but not during atrial fibrillation. If the patient has persistent atrial fibrillation during the procedure, electrical cardioversion can be done.[44]

Arrhythmogenic regions in pulmonary veins can be targeted by delivery of radiofrequency energy from the tip of the mapping catheter, to cause a localised area of necrosis. Traditionally, the aim of the mapping procedure has been to identify the location of arrhythmogenic foci (usually 2–4 cm inside the vein, measured from the pulmonary venous ostium), and to guide delivery of radiofrequency energy to those sites to render them electrically inactive. An alternative technique is to ablate the tracts of myocardium that extend from the left atrium into the pulmonary vein at the pulmonary venous ostium, thereby electrically isolating the pulmonary vein from the left atrium. This technique allows ablation during sinus rhythm or pacing and is not dependent on ongoing ectopy. It also provides a better endpoint for ablation, and can lower recurrence rates and incidence of ablation-induced pulmonary vein stenosis.[101] The idea has been extended to isolation of multiple veins near their ostia.[102] An alternative approach, in which circumferential lesions, guided by advanced mapping techniques, are created in the left atrium to isolate the four pulmonary vein ostia, has also been described.[103]

In patients with atrial fibrillation refractory to medical treatment, focal ablation done by skilled operators using conventional techniques can cure the arrhythmia in as many as 90% of patients with one focus, but in only 50% of patients with three or more foci. However, many ablation sessions are sometimes needed to achieve these results, especially in patients with more than one focus,[101,102] and success rates tend to be lower in patients with persistent atrial fibrillation than in those with paroxysmal atrial fibrillation, and lower in those with structural heart disease than in those without.[19] The prospect of isolating all four pulmonary veins in a safe and quick way by an empirical anatomical approach without the need for detailed mapping, is now the focus of technological development of appropriate catheters and ablative energy sources.

Surgery

On the basis of the findings that a finite mass of atrial tissue was needed to sustain atrial fibrillation,[22] and that atrial fibrillation was indeed an arrhythmia with multiple reentrant wavelets,[104] the Maze operation was devised. In this procedure the atria are dissected into segments, which are then rejoined by suturing, thereby reducing the confluent atrial tissue in which atrial fibrillation wavelets can rotate. By provision of a corridor from the sinus node to the atrioventricular node, sinus activation and atrial transport can be maintained.[104] Initial mortality rates were high, but with fewer incisions needed in Maze III, mortality has dropped to less than 3%, with greater than 95% success in abolishment of atrial fibrillation that was permanent in patients with structural heart disease.[105,106] Surgery for atrial fibrillation (mainly lone atrial fibrillation) restores quality of life to a level that matches that of the general population.[107] Because of its success, Maze-III surgery is now being done with surgery indicated for other reasons (including mitral valve repair and replacement) and, in a few centres, specifically for atrial fibrillation. Complications of the procedure include late-onset dysfunction of the sinus node and other atrial tachycardias. The Maze procedure restores right atrial function, but left atrial compliance and contribution to left-ventricular filling do not return to normal levels. Lines of conduction block can be created with hand-held radiofrequency ablation catheters to reduce the number of incisions with promising medium-term results.[108]

Control of ventricular rate

Digoxin is the most frequently used agent to control ventricular rate during atrial fibrillation. Unlike most other agents, it has weak positive inotropic properties, making many physicians comfortable with its use, even in patients with impaired ventricular function. However, digoxin is less effective than other agents at controlling ventricular rate,[109] especially during acute atrial fibrillation,[110] exercise,[111] or critical illnesses.[112] Furthermore, in patients with paroxysmal atrial fibrillation, digoxin does not control the ventricular rate, and could be associated with occurrence of longer paroxysms.[113]

Both intravenous and oral diltiazem can effectively control ventricular rate in patients presenting with atrial fibrillation and fast ventricular rates.[114,115] Both diltiazem and verapamil are better than digoxin at controlling ventricular response during exercise, and are associated with a small improvement in exercise capacity, without causing resting bradycardia or pauses.[116,117] The benefits of calcium-channel blockers and β-blockers compared with digoxin are especially pronounced in patients with impaired diastolic filling, such as those with mitral stenosis.[118] Combinations of digoxin with calcium-channel blockers or β-blockers might not only improve control of ventricular rate, both at rest and during exercise, but also improve exercise capacity, even in patients with underlying ventricular dysfunction.[119]

Chronic administration of amiodarone slows ventricular rate and reduces the burden of atrial fibrillation in patients with impaired ventricular function.[120] Data from uncontrolled studies[121] of acute atrial fibrillation suggest that intravenous amiodarone could also be moderately effective in controlling the ventricular response rate in atrial fibrillation in patients who are critically ill.[121]

Ablation of the atrioventricular node and implantation of a permanent pacemaker

This technique is still a last resort for patients with atrial fibrillation refractory to other treatments. By elimination of atrioventricular conduction, the ventricular rate can be completely controlled and regular ventricular contraction restored, both of which might help improve cardiac haemodynamics.[122] Since the atria continue to fibrillate, however, atrial contraction and atrioventricular synchrony are not restored, and the risk of stroke (and need for anticoagulation) persists. In controlled studies[123] of patients with chronic atrial fibrillation and heart failure, ablation of the atrioventricular node and insertion of a permanent pacemaker is more effective than drug treatment in control of palpitations and improvement of dyspnoea and quality of life, but not cardiac performance.[123] Mortality was unaffected by the procedure.[124] An alternative to complete ablation is modification of the atrioventricular node, which

is sometimes efficacious in relief of symptoms and control of ventricular rate in patients with atrial fibrillation.[125]

Prevention of thromboembolism

Reduction of risk of thromboembolism is very important in treatment of patients with atrial fibrillation. Treatment is clearly warranted in patients in whom the risk of thromboembolism is greater than the risk of complications that could result from anticoagulation. Reviews and guidelines on antithrombotic treatment in patients with atrial fibrillation have been published.[57,126,127] Antithrombotic treatment in patients presenting within 48 h of onset of atrial fibrillation and in those for whom cardioversion for restoration of sinus rhythm is planned has been discussed above. This section focuses on indications for long-term antithrombotic treatment in patients with atrial fibrillation.

Whether risk of thromboembolism differs substantially between patients with paroxysmal atrial fibrillation and those with chronic (persistent or permanent) atrial fibrillation is not clear, although investigators from one study[128] have suggested that risk might increase greatly in patients who progress from paroxysmal to chronic atrial fibrillation. Decisions about antithrombotic treatment should therefore be based mainly on variables proven to be associated with increased risk of thromboembolism (see below), and not necessarily on the temporal pattern of the arrhythmia.

Risk factors for thromboembolism in patients with atrial fibrillation

Data from the Framingham study[129] have shown that rheumatic heart disease that is complicated by atrial fibrillation is associated with a striking (18-fold) increase in risk of thromboembolism. In patients without rheumatic heart disease, atrial fibrillation raises thromboembolic risk by a factor of about six.[129–131] In these patients, incidence of ischaemic stroke without antithrombotic treatment is about 5% per year, but with large variation in this risk in different populations.[132–135] Both thromboembolic risk and the contribution of atrial fibrillation to the causes of ischaemic stroke increase with age. Multivariate analysis[133] of pooled data from five prospective studies of antithrombotic treatment in atrial fibrillation identified four independent risk factors for stroke—previous history of transient ischaemic attack or stroke, hypertension, age, and diabetes. Heart failure has also been identified as a risk factor.[136] In addition to these clinical factors, echocardiographic evidence of moderate or severe impairment of left ventricular systolic function in patients with atrial fibrillation is also an independent predictor of thromboembolism.[137]

Assessment of thromboembolic risk allows the clinician to select patients for anticoagulation whose risk of thromboembolism is much greater than the probable risk of bleeding complications with anticoagulant treatment. For example, patients younger than 65 years who have atrial fibrillation, but no thromboembolic risk factors, have a yearly stroke rate of 1%, and might not benefit from anticoagulation, whereas patients older than 75 years who have one or more additional risk factor for thromboembolism have a yearly stoke rate of 8% and are very likely to benefit from such treatment.[133]

Recommendations for antithrombotic treatment in patients with atrial fibrillation

Pooled data[133] from five randomised studies of patients with atrial fibrillation have shown that dose-adjusted oral anticoagulation with warfarin reduces risk of ischaemic stroke by 68%, and lowers mortality by 33%. However, since warfarin might increase haemorrhagic events, the risk-benefit ratio must be assessed for every patient individually. In patients who do not have valvular heart disease, the target international normalised ratio should be 2·0 to 3·0. Anticoagulation within this therapeutic range protects against ischaemic events, with a low risk of inducing haemorrhagic complications. The risk of haemorrhagic complications rises greatly when the international normalised ratio rises above 4·0[138] Unless contraindicated, oral anticoagulation can be recommended for patients in atrial fibrillation with any of the risk factors shown in panel 4.

Panel 4: **Risk factors for stroke, and indications for anticoagulation in patients with atrial fibrillation**

- Previous history of transient ischaemic attact or stroke
- Age > 65 years
- History of hypertension
- Diabetes
- Heart failure
- Structural heart disease
- Rheumatic or other significant valvular heart disease
- Significant left ventricular systolic dysfunction

Aspirin is less effective than warfarin in prevention of stroke in patients with atrial fibrillation, both in the size of risk reduction in placebo-controlled trials (22% *vs* 68%, respectively),[139,140] and in direct comparative studies against warfarin (36% reduction in stroke with dose-adjusted anticoagulation over aspirin).[140] Thus, at present, aspirin can only be recommended for patients with atrial fibrillation who have no additional risk factors for thromboembolism, or those who cannot safely take warfarin.

Conclusion

The past decade has seen many advances in understanding all aspects of atrial fibrillation. We are now able to cure a small but increasingly recognised proportion of patients with this disorder, with the promise of more widespread application of the evolving treatment strategies. The recommended treatment algorithm (figure 3) has greatly changed from that proposed by Narayan and colleagues[4] although anticoagulation remains a central feature in keeping morbidity and mortality to a minimum. Improving treatments and broadening indications for treatment of triggering sources and the perpetuating substrate, supported by appropriate randomised controlled trials, offer the prospect of a changing treatment focus in the next decade, with much less emphasis on controlling and combating atrial fibrillation, and a greater focus on cure.

Contributors

This report was written mainly by V Markides and N Peters, with R Schilling and P Kanagaratnam contributing their expertise to specific sections.

Conflict of interest statement

None declared.

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