TREATMENT OF ATRIAL FIBRILLATION

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Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. It may cause symptoms such as palpitations, dyspnoea, fatigue, dizziness or chest discomfort. Mortality risk has been reported to be twice as high when patients are in AF compared to sinus rhythm. As the incidence increases with age and the total number of elderly patients expands, the future clinical burden will be significant.[w1]

ARRHYTHMIA MECHANISMS

Mapping studies in fibrillating atria have confirmed the hypothesis of Moe and colleagues that AF is based on multiple wavelets of re-entry.[w2 w3] The stability of AF is mainly dependent on the number of wavelets that can circulate in the atria. In this respect, this explains why atrial dilatation is a risk factor for AF since the enlarged atria may accommodate more wavelets.[w4] Since the wavelength is determined by the product of refractory period and conduction velocity, a short refractory period or slow conduction facilitate the stability of AF. Interestingly, atrial refractory periods in patients with AF are shorter than in patients with sinus rhythm.[w5]

It has only recently been shown that AF itself causes shortening of the atrial refractory period. In an animal model Wijffels and colleagues demonstrated that repetitive induction of AF by atrial burst pacing led to the development of sustained AF in normal hearts. The hallmark of "AF begets AF" was a shortening of the atrial refractory period (electrical remodelling).[1] Further studies have shown that, in addition to electrical remodelling, structural and contractile remodelling also occurs.[w6 w7] These experimental observations explain why antiarrhythmic drugs (AADs) fail to terminate persistent AF[2] and why paroxysmal AF tends to become persistent or permanent.[w8]

For the induction and maintenance of AF, ectopic beats or rapid focal activity arising from the pulmonary veins play a much greater role than previously appreciated. This has opened up the therapeutic option of catheter ablation of focal AF.[3] In some patients the autonomic nervous system is involved in the genesis of paroxysmal AF. Enhanced sympathetic or parasympathetic tone may both shorten refractoriness and increase dispersion of refractoriness, and sympathetic drive is associated with atrial ectopy. Sympathetic adrenergic AF is relatively rare. It relates to stress and exercise and is frequently associated with coronary artery disease.[w9] Parasympathetic vagal AF occurs more frequently in otherwise normal patients. It predominantly starts during the night or after heavy meals.[w10]

The atrial substrate for AF frequently develops as a result of hypertension, coronary artery disease, or valvar disease, especially if these are complicated by heart failure. The patho-anatomic substrate mostly consists of fibrosis. In turn, fibrosis is associated with arrhythmogenic changes such as slowing and dispersion of conduction and an increase in heterogeneity of refractoriness.[w11] These notions comply with the fact that AF tends to start in the fifth to sixth decade in life, in particular the persistent form of AF. The continued presence of the patho-anatomic substrate explains why both paroxysmal and persistent AF recurs sooner or later in almost all patients.[w12 w13] In this respect, treatment of underlying heart disease is of major importance for long term prevention of AF.

ARRHYTHMIA MANAGEMENT: GENERAL CONSIDERATIONS

Antiarrhythmic treatment of AF can be divided in three strategies: termination of the arrhythmia in paroxysmal and persistent AF, maintenance of sinus rhythm in paroxysmal and persistent AF, and finally control of ventricular rate during paroxysmal, persistent, and permanent AF (table 1).

Removal of precipitating factors such as pericarditis, pulmonary embolism, thyrotoxicosis or excessive alcohol intake may result in disappearance of the arrhythmia. For this reason, a thorough diagnostic evaluation and optimal treatment of underlying heart disease should always precede considering a patient for cardioversion or maintenance treatment.

Antiarrhythmic drugs are given to suppress recurrences, but breakthrough arrhythmias may occur. Patients should be informed that a breakthrough arrhythmia does not necessarily mean drug failure. Antiarrhythmic drugs may cause ventricular proarrhythmia, conduction disturbances, and heart failure. Therefore, these patients should be informed about the symptoms associated with these AAD side effects.

Additional references appear on the Heart website—www. heartjnl.com

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Table 1 Classification of atrial fibrillation and therapeutic strategies

Type	Duration and character	Therapeutic strategy*
First episode	?	Conversion and prevention either with AAD or electrical cardioversion
Paroxysmal	< 48 hours, mostly spontaneous conversion (self terminating)	Conversion and prevention with VW class IC or III antiarrhythmic drugs. Rate control during arrhythmia
Persistent	>2–7 days, usually requires electrical cardioversion to restore sinus rhythm (non-self terminating)	Electrical cardioversion with/without antiarrhythmic drugs
Permanent	Restoration of sinus rhythm not feasible	Ventricular rate control

*Oral anticoagulation or aspirin as needed on the basis of risk factors (table 3) or in case of cardioversion.
AAD, antiarrhythmic drugs; VW, Vaughan Williams

Table 2 Clinical conditions and contraindicated antiarrhythmic drug treatment

- Heart failure (VW class I and III*)
- Coronary artery disease (VW class I)
- Left ventricular hypertrophy (VW class III*)
- Long QT interval (VW class I and III)
- Atrial fibrillation and WPW syndrome (verapamil/digoxin)

*Amiodarone is not contraindicated in heart failure and left ventricular hypertrophy.
VW, Vaughan Williams; WPW, Wolf Parkinson White.

In patients considered for AAD treatment pro-arrhythmia risk factors should be evaluated (table 2). If heart failure or angina pectoris develops, AADs may become contraindicated and therefore patients put on these agents should be followed regularly.

PHARMACOLOGIC AND ELECTRICAL CARDIOVERSION

Cardioversion of AF should be performed for the following reasons: relief of patient discomfort, prevention of thromboembolic events, and prevention of tachycardiomyopathy. In general, if AF lasts < 48 hours, AADs are highly effective and pericardioversion anticoagulation treatment is not needed. On the other hand, if AF duration is more than 48 hours the likelihood of pharmacological conversion decreases.[w14 w15] In these patients, direct current (DC) cardioversion after adequate anticoaguation treatment is preferred (fig 1). Anticoagulation treatment strategies will be discussed below.

Pharmacological conversion

Before considering AAD treatment one should bear in mind that up to 60% of patients with paroxysmal AF spontaneously cardiovert to sinus rhythm within 24 hours. Pharmacological cardioversion is considered in symptomatic patients who are haemodynamically stable. In unstable patients pharmacological cardioversion should be avoided for drug side effects. Electrical cardioversion may be useful but in any case rate controlling drugs should be given. For this purpose amiodarone is useful since it may serve two goals: rate control and cardioversion.

Basically, all AADs can convert short lasting AF to sinus rhythm. However, efficacy differs and the most successful agents are flecainide and propafenone.[w14 w16] Therefore, class IC AADs are first choice for pharmacological cardioversion of AF. However, owing to their negative inotropic effects, these agents should be avoided in patients with compromised ventricular function. In these patients amiodarone can be useful, although time to conversion is relatively long.[w17 w18] Ibutilide[4] is moderately effective but associated with a significant risk of torsade des pointes. Sotalol is rather ineffective but may reduce heart rate when adopting a wait-and-see approach. These class III agents tend to be much more effective in atrial flutter.[w19 w20] Digitalis, β blockers, and non-dihydropyridine calcium channel antagonists are ineffective for conversion of AF.[w21 w22]

Long term amiodarone pretreatment converts 15–40% of patients to sinus rhythm.[w17 w23]

External and internal DC cardioversion

Since the description of direct current electrical cardioversion of AF by Lown in 1962, this procedure has been widely used for restoration of sinus rhythm.[5] External cardioversion may be applied in the anterolateral or anteroposterior position and is successful in up to 90% of cases. Outcome depends on a carefully performed procedure using firm pressure on appropriately placed paddles and a sufficient amount of energy. Biphasic shocks are more effective than conventional monophasic shocks.[w24] To enhance shock efficacy, pretreatment with ibutilide may be applied.[6] As a last resort, patients with persistent AF unresponsive to external cardioversion may undergo internal catheter cardioversion.[w25]

MAINTENANCE OF SINUS RHYTHM

AF recurs in most patients, despite prophylactic antiarrhythmic treatment, and multiple pharmacological or electrical conversions are needed to maintain sinus rhythm. Risk factors for recurrence of paroxysmal AF include a history of frequent attacks, female sex, and the presence of associated cardiovascular disease.[w12] In patients with persistent AF most recurrences happen in the early post-cardioversion period. The following factors predict an unsuccessful arrhythmia outcome in persistent AF patients cardioverted to sinus rhythm: previous arrhythmia duration (> 1–3 years), age (> 60–65 years), atrial size (> 55 mm on echocardiogram), and rheumatic heart disease.[w13]

It has been questioned whether "rhythm control" is the preferred strategy for the treatment of AF. A recent study (PIAF—pharmacological pacing in atrial fibrillation)[7] showed that rate and rhythm control yielded similar clinical results with respect to symptoms, but exercise tolerance was better with rhythm control. Other studies are ongoing in Canada and the USA (AFFIRM— atrial fibrillation follow-up investigation of rhythm management)[w26] and the Netherlands (RACE—rate control versus electrical cardioversion for persistent AF).[w27]

Antiarrhythmic drugs for maintenance of sinus rhythm

A treatment strategy for the maintenance of sinus rhythm is shown in fig 2.

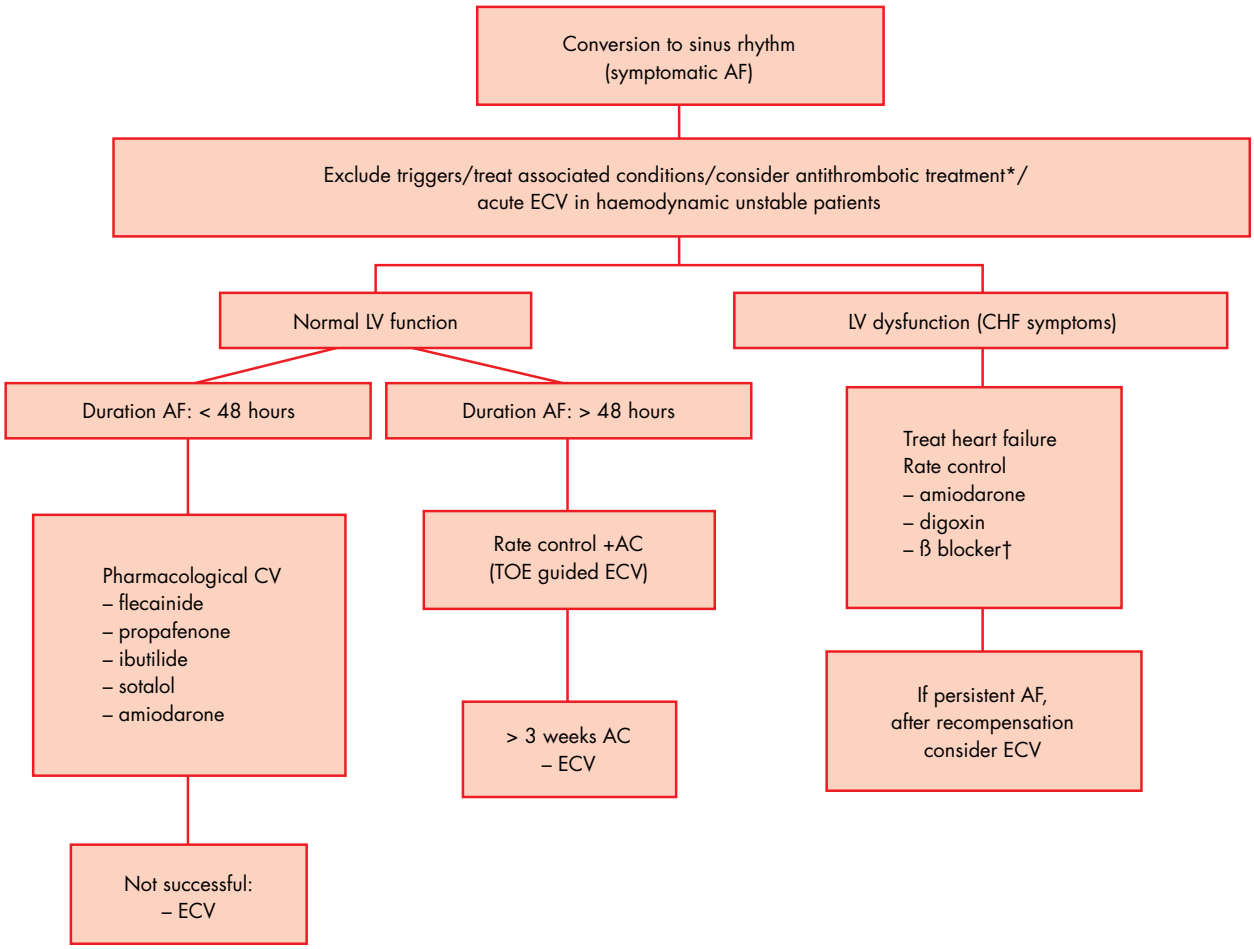

Figure 1 Treatment strategy for cardioversion of atrial fibrillation. *See table 3. †β Blockade including sotalol should be applied with caution in patients with left ventricular dysfunction to avoid aggravation of heart failure. AC, anticoagulation; AF, atrial fibrillation; CHF, congestive heart failure; ECV, electrical cardioversion; LV, left ventricular; TOE, transoesophageal echocardiogram.

Quinidine has been used most frequently for prevention of recurrences of AF. A meta-analysis showed increased mortality on quinidine compared to control.[8] Most drugs, including flecainide,[w28] propafenone,[w29] or sotalol[8] are equally effective and usually well tolerated. In a recent study, metoprolol appeared moderately effective and in patients with a recurrence, ventricular rate was better controlled by metoprolol than placebo.[w30] Of all available drugs, amiodarone is probably the most effective. In the CTAF (Canadian trial of atrial fibrillation) study patients assigned to amiodarone had a higher maintenance of sinus rhythm than those using sotalol or propafenone (fig 3). Adverse events occurred in 18% and 11% of patients using amiodarone and sotalol or propafenone, respectively. Unfortunately, the design of the study could not address the potential side effects associated with long term use of amiodarone.[9] Thus, it may well be that a higher breakthrough attack rate with fewer side effects is preferred above a low attack rate but at the cost of severe amiodarone side effects. This holds true even more since side effects of amiodarone cannot be predicted. Therefore in many patients amiodarone will remain second or last choice.

Recent evidence suggests that verapamil enhances efficacy of prophylactic AAD treatment in patients undergoing electrical cardioversion.[w31] Episodes of AF associated with high vagal activity are usually suppressed by disopyramide or flecainide, but worsened by digoxin or β blockers. Conversely, adrenergic AF should be treated with β blockers.[w10] In sick sinus syndrome, AADs should be avoided unless a pacemaker has been implanted. A pacemaker may even help to reduce the attack rate in these patients.

AF in the setting of chronic heart failure is difficult to treat and most agents are contraindicated under those circumstances. In a subgroup analysis of data from CHF-STAT (congestive heart failure survival trial of antiarrhythmic therapy), amiodarone reduced the incidence of AF over four years from 8% to 4%. Conversion to sinus rhythm occurred in 31% of 51 AF patients on amiodarone versus only 8% on placebo and this was associated with significantly better survival.[10] Similarly, dofetilide, initiated in hospital, was associated with a lower incidence of AF (1.9%, 11 of 556 patients) than placebo (6.6%, 35 of 534 patients) after an average of 18 months. On dofetilide, 25 cases of torsade-de-pointes occurred (three quarters of which occurred within three days after starting treatment). Mortality was equal in both groups (41% and 42%), but dofetilide was associated with a significantly reduced hospital readmission rate for heart failure.[11]

NON-PHARMACOLOGICAL MANAGEMENT OF AF

Surgical treatment

The Maze procedure, introduced in 1987 by Cox, preserves atrial contractility and is the most frequently used of all surgical techniques.[12] The rationale for the Maze procedure is that strategically placed surgical incisions interrupt potential multiple wavelet re-entry circuits, thereby preventing or terminating AF. The latest modification, the Maze III, consists of

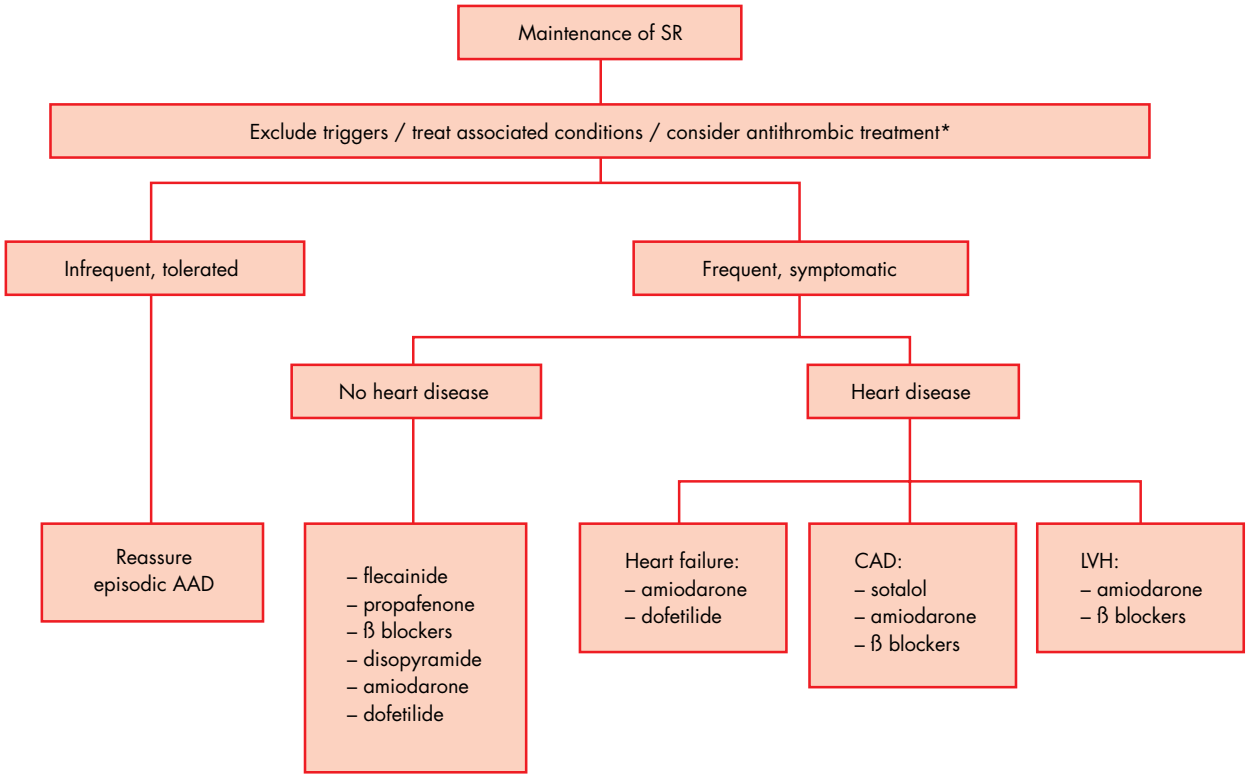

Figure 2 Treatment strategy for maintenance of sinus rhythm (SR). *See table 3. AAD, antiarrhythmic drugs; CAD, coronary artery disease; LVH, left ventricular hypertrophy.

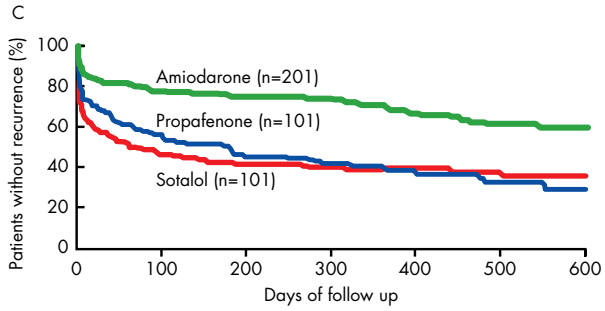

Figure 3 Kaplan-Meier curves showing percentage of patients without recurrence of atrial fibrillation who were treated with either amiodarone, propafenone, or sotalol. Reproduced from Roy *et al*,[9] with permission of the Massachusetts Medical Society.

removal of both atrial appendages, isolation of the pulmonary veins, and multiple incisions in both atria. During a 10 year follow up period, Cox and colleagues reported very favourable results in 201 patients[w32] which was confirmed by others.[w33]

New modifications—for example, using radiofrequency catheter ablation techniques—are being evaluated and may contribute to a wider acceptance of this type of treatment of AF.[w34]

In patients with symptomatic AF, who are to undergo surgical correction for coronary artery disease or valvar heart disease, a concomitant Maze should be considered. There are, however, only limited data to support its application and the prolonged procedure time adds to the operative risk.

Radiofrequency catheter ablation of focal AF

Haissaguerre and colleagues described a group of 49 patients with drug refractory AF in whom an ectopic atrial focus or foci could be identified during a diagnostic electrophysiological study (fig 4).[3] Foci were predominantly located within the pulmonary veins. Application of radiofrequency energy to these foci abolished atrial ectopic activity. After a mean (SD) of 8 (6) months of follow up, 62% of patients had no further attacks of AF and all patients use of antiarrhythmic drugs was discontinued.

Ideal candidates for focal AF ablation are young patients with frequent paroxysms of AF initiated by rapid monomorphic atrial tachycardias. Long term complications include pulmonary vein stenosis, pericardial effusion, and cardiac tamponade.[w35] Other techniques like pulmonary vein exclusion and linear ablation are still investigational.[w36]

Pacing strategies to prevent or terminate AF

In several clinical situations atrial pacing has been shown to prevent the development of AF. In patients with sick sinus node disease, AAI pacing proved to be superior to VVI pacing in reducing the incidence of AF.[13 w37] Recent studies also suggest that continuous atrial pacing, especially in combination with β blockers, may prevent postoperative AF. Uncertainty exists about the optimal site and mode (single/multisite) of pacing.[w38 w39] Furthermore, it is not clear whether pacing strategies to prevent AF will also result in a subsequent reduction in thromboembolic events. Atrial pacing for prevention of AF is still an experimental treatment and the results of ongoing trials will determine its clinical value.

Pacing may also be used to terminate AF. Some dual chamber pacemakers are equipped with atrial tachycardia/fibrillation detection and termination algorithms. Results so far demonstrate a reduction in arrhythmia burden in treated patients.[w40 w41] Interestingly, the stored electrograms of AF initiation revealed a relatively high incidence of organised atrial tachycardias. Antitachycardia pacing was most successful in

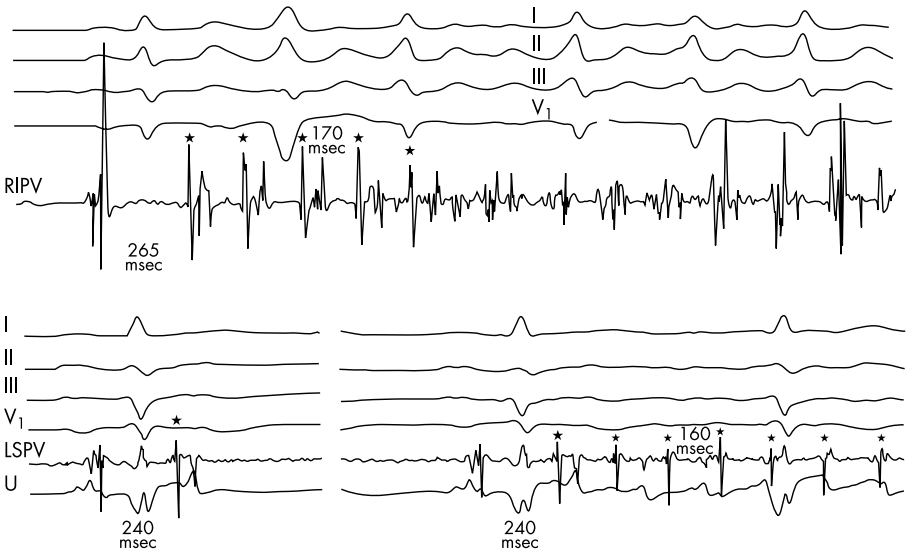

Figure 4 Two examples of the onset of atrial fibrillation from foci in a right inferior pulmonary vein (RIVP) and a left superior pulmonary vein (LSVP). In the upper panel, sinus rhythm is followed by a burst of five ectopic beats from the right inferior pulmonary vein, with coarse atrial fibrillation on the surface ECG. In the lower panel, two tracings with ectopic activity from the left superior pulmonary vein are shown. On the left an ectopic beat with a coupling interval of 240 ms does not induce atrial fibrillation. In the same patient (on the right), a train of spike discharges (asterisk) at a cycle length of 160 ms initiates atrial fibrillation. Reproduced from Haissaguerre *et al*,[3] with permission of the Massachusetts Medical Society.

these types of AF.[w41] In patients with a history of AF and an indication for permanent pacing or implantable cardioverter-defibrillator (ICD) treatment, an antitachycardia pacemaker or a dual chamber ICD with antitachycardia pacing capabilities may be considered, respectively. Optimisation of patient selection criteria (for example, based on initiation pattern) may improve the efficacy.

Atrial implanted cardiac defibrillator

Wellens and colleagues reported the initial experience with the atrial ICD or atrioverter in 51 patients with recurrent episodes of AF who had not responded to antiarrhythmic drugs.[14] During a mean follow up period of 259 (138) days, 96% of 227 episodes of AF were cardioverted successfully. No ventricular pro-arrhythmia events occurred.

The ICD can detect and treat AF early after initiation, which may improve long term arrhythmia outcome. However, important disadvantages exist. First of all, AF is not prevented. Furthermore, the shock is rather painful. Finally, at present, no stand alone atrial ICD is available. Combined atrial and ventricular ICDs are, however, available and may be useful in selected patients, especially in those who need a ventricular ICD and suffer from infrequent but poorly tolerated attacks of AF.

CONTROL OF VENTRICULAR RATE

Control of ventricular rate aims at reducing signs of circulatory insufficiency and prevention of tachycardiomyopathy.[15] This can be achieved by negative chronotropic drugs or atrioventricular node ablation and insertion of a pacemaker. Although the targeted heart rate is unclear, it is reasonable to aim at heart rates under 90 beats/min in resting conditions and below 110 beats/min during light and moderate exercise. Perhaps more importantly, adequate rate control during daily exercise should be assessed using 24 hour Holter recordings.

Most commonly used agents are calcium channel antagonists, β blocking drugs, and digoxin. Historically, digoxin has been the drug of choice. Amiodarone should be avoided for its significant side effects. Surprisingly, only a limited number of studies evaluated the efficacy of these agents. Farshi and colleagues included 12 patients with AF duration of at least one year duration who were randomly assigned to digoxin (0.25 mg), diltiazem (240 mg), atenolol (50 mg), digoxin + diltiazem (0.25 mg + 240 mg), and digoxin + atenolol (0.25 mg + 50 mg). Ventricular rate control was evaluated with 24 hour Holter recordings and exercise testing. Combination therapy of digoxin and atenolol was superior to all other regimens during exercise as well as during daily activities. Digoxin as a single agent proved less effective, especially during exercise testing.[16] Nevertheless digoxin usually suffices if needed at all in the sedentary elderly. In active patients excessive reduction of exercise heart rate is not desirable since it limits exercise capacity. In these patients β blockade with or without digoxin is usually sufficient to control resting heart rate while preserving a reasonable response during daytime exercises. In patients with an accessory atrioventricular pathway (Wolf-Parkinson-White syndrome) paroxysmal AF may be associated with an excessively high heart rate. Use of digoxin, verapamil or a β blocker as rate controlling drugs should be avoided. Intravenous flecainide will reduce heart rate and may provide conversion. In the haemodynamically unstable patient immediate cardioversion is indicated.

Ablate and pace

Patients who remain symptomatic despite adequate negative chronotropic drugs, or those who cannot tolerate these drugs, may undergo atrioventricular node ablation with pacemaker insertion.[15 w42] Prospective data have shown an increase in left ventricular function after atrioventricular node ablation, especially in patients with significant baseline ventricular impairment.[w43 w44] This was parallelled by increased exercise duration, higher quality of life, and reduced health care use.[w45 w46] If AF is paroxysmal DDD(R) pacing mode with mode switch is indicated; in permanent AF a VVI(R) pacemaker suffices.

ANTICOAGULATION IN AF

Long standing non-rheumatic AF is associated with a 5.6 fold increase in risk of thromboembolic complications.[w47] Several predisposing factors for stroke have been identified from pooled data sets: rheumatic heart disease, hypertension, prior strokes or transient ischaemic attacks, diabetes mellitus, recent heart failure, enlarged left atrium, impaired left ventricular function or age > 65 years.[w48 w49] Large trials have been conducted and have convincingly demonstrated the benefit of adequate anticoagulation (international normalised ratio 2–3) in terms of reducing the risk of ischaemic stroke.[w50–57] The above mentioned risk factors should be taken into account irrespective of the rhythm itself (sinus rhythm or

Table 3 Antithrombotic treatment in patients with atrial fibrillation

Oral anticoagulation (optimal INR 2–3):
- ▶ Rheumatic heart disease (mitral stenosis)
- ▶ Prosthetic heart valve
- ▶ High risk patients:
  - –history of CVA or TIA
  - –hypertension
  - –diabetes mellitus
  - –heart failure
  - –age >65 years
  - –echocardiogram: LV dysfunction, HCM
  - –thyrotoxicosis

Aspirin (75–325 mg/daily):
- ▶ "Lone" atrial fibrillation
- ▶ No risk factors
- ▶ Age <65 years

Contraindication for oral anticoagulation

CVA, cerebrovascular accident; HCM, hypertrophic cardiomyopathy; INR, international normalised ratio; LV, left ventricular; TIA, transient ischemic attack.

AF) and the type of AF (paroxysmal versus persistent versus permanent) (table 3).

In both electrical and pharmacological cardioversion the risk of thromboembolic complications surrounding the cardioversion ranges from 1–5.3%.[w58] Therefore, it is now generally accepted that in patients with AF lasting 48 hours or more, adequate anticoagulation should be maintained at least three weeks before and four weeks after cardioversion. Pretreatment before the shock may be avoided after exclusion of intra-atrial thrombi using transoesophageal echocardiography.[17] Post-cardioversion continuation of anticoagulation is necessary since transient mechanical dysfunction of the atria is believed to predispose to the formation of intra-atrial thrombi.

SUMMARY AND PERSPECTIVES

AF often results from underlying heart disease. When AF occurs, electrophysiological, structural, and contractile remodelling promotes its maintenance. Therefore, when treating AF, underlying heart disease should be managed first. Termination of AF can be achieved by using pharmacological or electrical cardioversion. To suppress arrhythmia recurrences or occurrences antiarrhythmic drugs remain the first choice of treatment. New treatment strategies including radiofrequency catheter ablation, surgical techniques, and atrial pacing are of potential value for the treatment of AF. Despite these novel advances AF persists or recurs frequently. Large trials are being conducted to answer the question whether "rhythm" or "rate" control is the optimal treatment for AF. The results of these trials will have important implications for the treatment of AF.

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