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HOW IS SINUS RHYTHM MAINTAINED IN PAROXYSMAL ATRIAL FIBRILLATION?*

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While the choice of appropriate treatment of all varieties of atrial fibrillation (AF) can be difficult, when the disorder occurs as self-terminating paroxysms some problems particular to this variety of AF arise. For permanent AF, only rate-control therapy and warfarin are required, and with persistent AF the term of prophylactic therapy can expire after one or two years. With paroxysmal AF, long-term treatment with arrhythmia-suppressing treatment is envisaged in a patient population that is younger and more likely to be free of other heart disease than those with persistent or permanent AF (50% have 'lone' paroxysmal AF, versus 20% and <10% for persistent and permanent AF respectively).

A clinical perception exists that paroxysmal AF is a precursor, by months or a few years, of permanent AF. Many patients, however, continue to suffer from purely paroxysmal AF for many years and, in any case, paroxysmal AF needs consideration for prophylactic antiarrhythmic drug therapy in the meantime. Current drug therapy is limited by side-effects and incomplete efficacy, and persisting medical concerns regarding proarrhythmic potential of drugs. Given the limited efficacy of current treatments, the possibility that, had effective treatment been offered at an early stage, the eventual outcome would have been different cannot be excluded. Attractive non-pharmacological strategies are emerging, and these may be more effective and cheaper in the long-term than antiarrhythmic drug therapy, but so far systematic evidence is too sparse and follow-up too short for definitive recommendations to be made from these trials.

This article is a systematic review of what is currently established regarding the efficacy of both pharmacological and interventional treatments for paroxysmal AF. Treatments have been applied to rather diverse populations, making direct comparisons difficult. None-the-less, a considerable amount is now known and several recommendations can be made.

AIMS OF TREATMENT

Atrial fibrillation occurs in distinct forms; it may usefully be classified using the '3P' classification for chronic AF (Figure 1).[1,2] This divides the disorder into paroxysmal, where AF generally self-terminates; persistent, where AF does not spontaneously convert but reverts readily to sinus rhythm with electrical or pharmacological cardioversion; and permanent, where cardioversion is not possible or the patient or doctor prefer to allow the AF to continue. Inherent in this classification are the goals of therapy: for persistent AF, to restore sinus rhythm and prevent recurrence of AF; and for permanent AF, to control ventricular rate and prevent thromboembolism.

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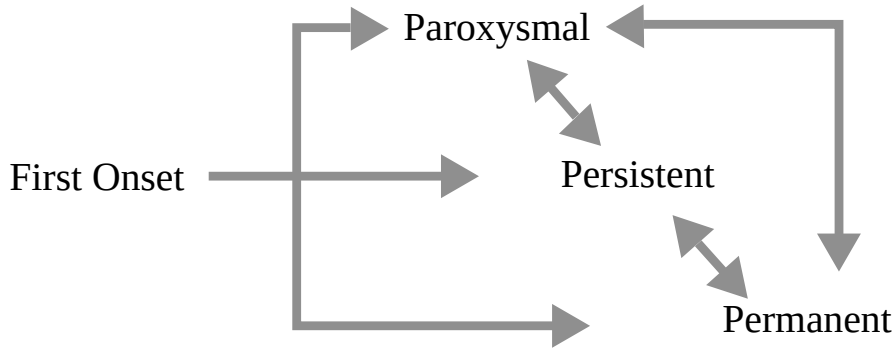

FIGURE 1
Progression and regression of atrial fibrillation. Where AF continues for more than 48 hours, or recurs after first onset has terminated, it has by definition become chronic AF. This is sub-classified as paroxysmal, persistent and permanent, and with time a patient may move between these types of AF.

Paroxysmal AF is not usually an immediately life-threatening arrhythmia, but does give rise to substantial morbidity and mortality. The goals of therapy are to improve symptoms and general well-being whilst also extending the prognosis, and to prevent long-term health deterioration. While the disorder is paroxysmal in nature, patients are seldom completely well between attacks. As with the persistent and permanent forms of AF, paroxysmal AF can cause complications such as a tachycardia-induced cardiomyopathy[3] or stroke.[4] Most adverse effects of treatment are present throughout the period of treatment, and thus drug side-effects and complications of non-pharmacological treatments are an important issue. Finally, there is a psychological morbidity attached to having the disorder, arising from justified or unjustified concerns regarding implications for long-term health. In many patients activity is severely restricted by fear of provoking or suffering from an AF episode. Patients often feel insecure because of their inability to control or even predict attacks (an 'external locus of control').

The traditional objective of medical interventions is the prevention of AF, but this is only one of several means by which symptoms may be reduced (Table 1). That the maintenance of sinus rhythm is not the only modality for improving symptoms is explicit in some therapies, for example, implantation of a dual-chamber mode-switching pacemaker following AV nodal ablation (discussed later). In many trials the benefit of treatment is measured by symptomatic improvement, and whether the benefit shown is derived from suppression of paroxysmal AF or from other mechanisms is often unknown. In one of the few insights into this issue, Page *et al* showed that only approximately one in twelve episodes of paroxysmal AF was symptomatic.[5] By contrast, episodes of paroxysmal supraventricular tachycardia were always symptomatic.

TREATMENT

A major impact of paroxysmal AF results from psychological morbidity. It is not unusual for patients to believe that their 'heart will stop', or a 'heart attack' will occur during episodes, and such fears should be firmly allayed. AF is unpleasant and has an impact varying from minor to significant, but major health risks, such as

TABLE 1
Mechanisms of reducing symptoms from paroxysmal AF.

Mechanism	Comment / Examples
Reduce frequency of paroxysmal AF	Presumed predominant mechanism of benefit of anti-arrhythmic agents
Reduce duration of paroxysmal AF episodes	Possible secondary mechanism of benefit of anti-arrhythmic agents.
Reduce heart rate during episodes	Definite effect of beta blockers, verapamil, diltiazem and may occur with some other agents. Digoxin does not slow heart rate at onset of paroxysmal AF.[6]
Regularise rhythm during paroxysmal AF	Implantation of a dual chamber mode switching pacemaker with AV nodal ablation which works by providing a regular ventricular response at a physiologically appropriate rate. Some benefit of drugs may be by this mechanism, but is poorly studied.
Other mechanisms (e.g. alterations in peripheral vascular responses), which may convert symptomatic to asymptomatic episodes	Whether or not tachycardia causes syncope appears be related to peripheral vascular responses, rather tachycardia rate.[7] Modulating neurohumoural response may provide patient benefit.

thromboembolism and tachycardiomyopathy, are preventable with appropriate treatment, suitable screening and follow-up. Specific therapy may be unnecessary if attacks are infrequent, tolerated well, and short-lasting. However, if the frequency or duration of attacks increases, intervention is needed to prevent further deterioration, and the development of persistent or permanent AF.

Improvement of long-term outcome by successful suppression of paroxysmal AF seems likely and is supported by indirect data, but no definitive proof exists. Supportive evidence includes animal data that show that AF induces changes in the atria that favour further episodes;[8] that increasing duration of AF promotes atrial dilatation[9] which is known to predispose to AF;[10] and preliminary reports of increasing intervals between AF episodes following prompt cardioversion.[11]

Pharmacological methods

A wide range of drugs has been shown in clinical trials to be effective in treating atrial fibrillation (Table 2). The apparent merits of individual agents must be seen in the context of the general limitations of the available studies. Heterogeneous populations are often included, with some authors using the term paroxysmal AF for any patient who has a recurrent form of AF (i.e. both paroxysmal and persistent AF). Other studies have explicitly included mixed populations, such as patients with regular paroxysmal supraventricular tachycardia or persistent AF. Outcomes are sometimes presented separately, but the numbers in subgroups are usually small. Many, if not most, trials are of limited size, which hinders the proper evaluation of drug efficacy and safety. While some individual trials were well designed, much of the current data is flawed by lack of placebo control or by having endpoints that are ill-defined, often subjective, and which often vary considerably between individual trials.

TABLE 2
Selected trials of drug therapy for paroxysmal AF.†

Trial Drugs	Trial Design	Efficacy*	Side-effects
Flecainide vs. Placebo[12]	Rand; Blind, Crossover	Time to first recurrence: flec. = 14.5 days; placebo = 3 days. Interval between attacks: flec = 27.0 days; placebo = 6.2 days	Flecainide +, Placebo = 0
Flecainide vs. Quinidine[13]	Rand; Open, Crossover	100% suppression in 50% of patients vs. 16-32% with quinidine.	Flecainide 0, Quinidine ++
Flecainide vs. Propafenone[14]	Rand; Open, Parallel	Proportion discontinuing therapy similar because of inadequate response: flec = 23%; propaf = 24%	Flecainide +, Propafenone ++
Propafenone vs. Placebo[15]	Rand; Blind, Crossover	Probability of treatment failure was 6 times higher on placebo than propaf, high dose propaf more effective but ↑↑ SE	Propaf (low) + Propaf (high) ++
Propafenone vs. Placebo[16]	Rand; Open, Crossover	Proportion of days on which attack occurred; propaf = 27; plac = 54. Despite large number minor SE with propaf, early crossover (due to SE or poor response) much higher on plac (45% vs. 14%)	Propaf ++
Propafenone vs. Quinidine[17]	Rand; Blind, Crossover	Proportion with > 75% reduction in attacks: propaf = 87%; quinidine = 46%	Propaf +, Quinidine +
Propafenone vs. Sotalol[18]	Rand; Blind, Crossover	Proportion with > 75% reduction in attacks: propaf = 79%; sotalol = 76%	Propaf +, Sotalol +
Propafenone vs. Sotalol[19]	Rand; both parox. and persist. AF	Efficacy the same overall. Data regarding paroxysmal AF not reported separately, but similar efficacy in subgroups noted	Propaf ++, Sotalol +++ (††)
Amiodarone[20]	Uncontrolled; Rx resist pt.	Effective in 9 of 13 patients who had failed at least 2 previous agents	Amiod ++

†Due to the varying size, design, inclusion criteria and population mixes, it is not feasible to create a comprehensive unified list. The studies included fulfil one or more of the following criteria: fully-reported; large sample; 'good' design; novel or important results.
Other trials are drawn to the attention of interested readers: Martin *et al* (amiodarone vs. disopyramide);[21] Murgatroyd *et al* (digoxin vs. placebo, atenolol vs. disopyramide vs. placebo);[22,23] Naccarelli *et al* (flecainide vs. quinidine, findings similar to Van Wilk[13]),[24] Pritchett *et al* (propafenone vs. placebo);[25] Pietersen *et al* (flecainide vs. placebo).[26]
Key: *Due to differing outcome measures, representative findings from each trial are quoted.
Trial Design: Rand=randomised; Open=open-labelled; Blind=double-blind; Uncontrolled=no control group, randomisation or crossover; Rx resist pt.=therapy-resistant patients.
Side-effects:+=requiring discontinuation in 5-12%; ++=requiring discontinuation in 13-25%; +++=>25% or deaths due to therapy.
††There were two deaths on sotalol, and one non-fatal ventricular arrhythmia on each drug, but AF subtype (parox. or persist) not clear.

Safety concerns in pharmacotherapy for AF have arisen from the increased mortality in those prescribed antiarrhythmic drugs in some,[27-29] but not all,[30,31] post-infarction trials. A meta-analysis of quinidine for AF patients suggested that this agent may be associated with an increased risk of death,[32] but other studies of patients with supraventricular arrhythmias are reassuring.[33] Several different arrhythmias considered related to the use of antiarrhythmic drugs are known (Table 3). The overall impression from investigation of these is that with proper drug selection, based on patient criteria, antiarrhythmic therapy is safe as long as treatment is monitored with electrocardiography, regular serum electrolyte checks and other investigations as appropriate.

A specific concern in patients with paroxysmal AF is the occurrence of atrial flutter with one-to-one ventricular conduction (Figure 2). This may occur in any patient who suffers from paroxysmal AF, and is probably the most frequent cause for a broad complex tachycardia in this scenario, but is none-the-less often mistaken for ventricular tachycardia. Several agents used to treat paroxysmal AF also cause Torsades-de-Pointes, including sotalol, quinidine and the new Vaughan Williams class III antiarrhythmic drugs. Vigilance is required to ensure that hypokalaemia is prevented, that the resting ECG QT interval is monitored, and that high doses or inappropriate drug combinations are avoided (e.g. co-administration of anti-histamines). Some patient groups are at particularly high risk of Torsades, like those with ventricular hypertrophy; the arrhythmia is also more common in young females.

Of the agents listed in Table 2, flecainide has been subjected to the largest number of randomised and non-randomised studies in this field; it is generally well tolerated

TABLE 3
Types of pro-arrhythmia seen during the drug therapy of paroxysmal AF.*

Pro-arrhythmic risk	Drug	Population at risk / notes
VT / VF	Class 1 AAD's (Flecainide, propafenone, etc.)	Any patient with ventricular dilatation, scarring (prior MI or surgery) or ischaemia
1 to 1 atrial flutter (see text)	Class 1 AAD's (Flecainide, propafenone, disopyramide etc.)	Most patients with AF, but particularly younger patients, those with good AV nodal conduction, and those with documented atrial flutter. Consider routine co-administration of AV nodal blocking drug (e.g.diltiazem)
Drug induced Torsades-de-Pointes	Sotalol, Quinine, and newer Class 3 agents	Left ventricular hypertrophy (e.g. hypertension), hypokalaemia and hypomagnesaemia (e.g. diuretic use), young females.
Symptomatic bradycardia and Strokes-Adams attacks	Beta-blocking agents (including sotalol and amiodarone), verapamil/diltiazem and probably class 1c agents	Older patients, and in particular, those with sick sinus syndrome as the primary cause of paroxysmal AF

*Avoidance if inappropriate prescribing largely circumvents the risk of pro-arrhythmia, but great caution is required to prevent arrhythmic sudden death. Measures for prevention are tailored to the clinical circumstances: absolute avoidance of class 1 agents following myocardial infarction and class 3 agents where significant left ventricular hypertrophy is present; but class 1 agents may be used with mild ventricular dilatation and class 3 agents in young women given careful ECG and Holter monitoring.

AAD=autoarrhythmic drugs; VT= ventricular tachycardia; VF= ventricular fibrillation.

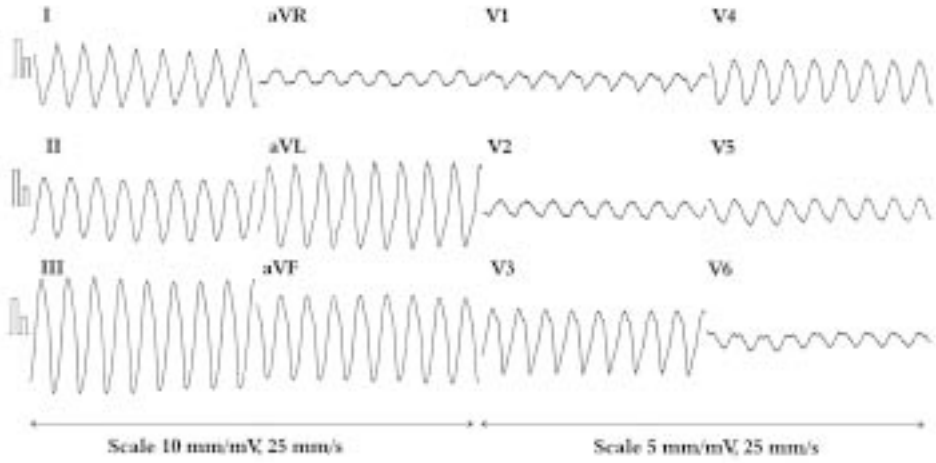

FIGURE 2

ECG of broad complex tachycardia in a patient with paroxysmal AF, no structural heart disease and on flecainide. A Holter recording during the same admission showed periods of sinus rhythm, narrow complex AF, broad complex AF and identical morphology regular broad complex arrhythmia. This strongly supports the interpretation that this ECG represents atrial flutter with one-to-one ventricular response. Intraventricular conduction delay, giving rise to broad complexes, results from flecainide treatment and from the high ventricular rate.

and is therefore recommended as a first-line agent (with due consideration given to pro-arrhythmic risks - Table 3). Propafenone and sotalol have also been shown to be efficacious and generally well-tolerated in well-conducted studies, and may equally be used as first-line agents. Disopyramide and quinidine are effective but more frequently associated with side-effects and should be reserved for second-line use. Other agents, such as digoxin, beta blockers, and other anti-arrhythmics have insufficient data to support evidence-based recommendation, but may be employed on an empiric basis. Finally, the use of amiodarone is only supported by uncontrolled studies but, despite this, it is believed to be highly effective. Amiodarone is usually recommended for second- or third-line use, although physicians increasingly use this therapy as the treatment of choice. It is proper to reserve it for those who fail other agents because of the drug's numerous side-effects most of these are minor (hypersensitivity to sunlight, sleep disturbance and benign corneal microdeposits) but some are potentially life-threatening (pulmonary fibrosis). It deserves early consideration in the elderly and in those with severe myocardial dysfunction.

The choice of drugs must be individualised on the basis of efficacy and tolerability. An initial choice of agent can be based upon the clinician's familiarity and preference, but sometimes several agents at varying doses must be tried before the optimal treatment is found. A role for prevailing autonomic tone in precipitating AF onset has been described for some patients. In those where high vagal tone precipitates AF (e.g. sleep

onset, resting onset or post-prandial onset), agents with vagolytic actions (e.g. disopyramide) are often effective; while in those with a presumed adrenergic onset (exercise- or stress-induced AF), a favourable response to beta-blocking agents can be expected. This hypothesis has not yet been validated in a fully reported randomised clinical trial, although some observational data are available.[34]

A final drug strategy is the 'pill-in-the-pocket' approach. This entails the patient taking no regular medication, but one or two oral doses of an antiarrhythmic agent when they experience AF. The aim is to shorten the duration of the episodes, and may be useful for a proportion of patients. It can only be employed after the drug given in this way has been documented not to produce adverse effects by supervised administration (e.g. by attending an A&E department or CCU for monitoring on one or more occasions) and where absolute patient compliance with the prescribed dose is expected.

Non-pharmacological methods

Non-pharmacological strategies treat paroxysmal AF either by reducing the occurrence of episodes, by facilitating the termination of episodes, or by reducing symptoms arising from episodes. Most non-pharmacological techniques are still investigational (Table 4); only three have entered clinical practice in more than a few research centres: surgical 'Maze', 'ablate and pace', and the 'atrioverter'.

TABLE 4
Non-pharmacological Treatments for Paroxysmal AF.

Treatment	Description	Benefits	Drawbacks
Atrial pacing algorithms	Atrial pacing performed to overdrive suppress arrhythmias and/or ensure consistent capture of theatrial by the pacemaker	• Potentially preventative	• Unproven • Not effective for all
Novel atrial pacing methods	Lead implanted at unusual sites or multiple leads to suppress AF	• Potentially preventative	• Unproven • Complicated • Not effective for all
Ablation of underlying focal	Case reports describing several patients in whom AF atrial tachycardia was initiated by an atrial tachycardia.	• Potentially curative	• Uncertain how common this mechanism is
Surgical MAZE procedure	See text	• Potentially curative • Available	• Major surgery required • Post-procedure sinus node dysfunction
Radiofrequency ablation MAZE procedure	Similar principle to surgical maze, but performed by creation of radiofrequency ablation lines	• Potentially curative	• Long difficult radiofrequency ablation • Systemic thromboembolism and pulmonary venous obstruction
AV nodal ablation with implantation of mode transport switching dual chamber pacemaker	See Figure 3	• Effective • Available	• Does not maintain atrial function (risk of thromboembolism remains,and atrial lost during AF renders patient pacemaker dependent
Implantable atrial defibrillator	Implanted device which detects AF and delivers a cardioverting shock between coils in the right atrium and coronary sinus. A ventricular lead provides sensing to ensure shock is precisely R wave synchronised and also backup pacing.	• Effective • Available	• May not prevent AF episodesdefibrillator • Pain during defibrillation

The surgical 'Maze' procedure has been developed and refined over several years.[35,36] Multiple adjacent corridors of atrial tissue are created surgically (narrow and intertwining, hence the term 'maze'). These corridors conduct the sinus impulse to all parts of the atrium without being sufficiently wide to allow re-entry of the impulse and thus to create sustained AF. The surgery is effective but has drawbacks: the morbidity associated with open heart surgery and a high incidence of post-operative sinus node dysfunction. It has been used for all forms of AF. The operation is often performed during mitral valve replacement or repair, when the additional surgery is of little adverse consequence to the patient.[37-39]

In patients with paroxysmal AF which is resistant to drug therapy, a rapid and irregular ventricular rate is often the major contributor to symptoms, and AV-nodal ablation and dual chamber pacemaker implantation is an option (Figure 3). This procedure improves symptom scores and quality-of-life measurements in the majority of patients. Drawbacks include the need for AV nodal destruction (rendering the

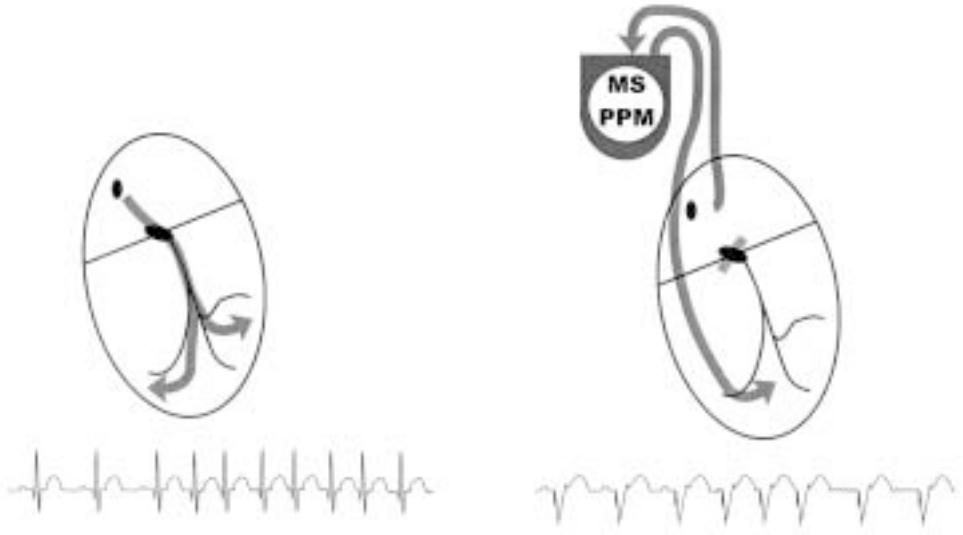

FIGURE 3

The principle supporting the treatment of AF by AV nodal ablation and implantation of a mode-switching dual chamber pacemaker. (a) Normal cardiac activation originating in the sinus node, travelling slowly via the atrioventricular node, and then activating the ventricle via the His-Purkinje system. The lower trace shows AF beginning, with the atrial impulses transmitted to the ventricle at rates of up to 220 bpm. (b) Shows the situation after AV nodal ablation with implantation of mode-switching pacemaker (MS PPM). During sinus rhythm, atrial events are detected and result in a stimulus being delivered to the right ventricular apex on a one-to-one basis. Conduction via the AV node can no longer occur. When AF begins, these atrial signals are transmitted to the ventricle close to the pacemaker's upper tracking limit (i.e. the highest rate it is allowed to pace the ventricle). After three beats the algorithm within the pacemaker has decided that the rate is too fast and irregular to be sinus rhythm. It therefore ignores the atrium and paces the ventricle at an appropriate rate determined by the patient's activity. It continues to monitor the atrium and will switch back to its normal pacing mode when sinus rhythm returns.

patient pacemaker dependent for life), the failure to produce symptomatic benefit in some, and increased likelihood of developing permanent AF in others, with its attendant thromboembolic risk.[40] The time required for the pacemaker to switch from a tracking mode (e.g. DDDR) to a non-tracking mode (e.g. DDIR or VVIR) and back again varies between devices and, in general, devices capable of rapid 'mode switching' seem to be superior, but this has not been comprehensively demonstrated.

An implantable atrial defibrillator (atrioverter) has been developed, building on the experience with implantable cardioverter defibrillators for ventricular tachyarrhythmias, and the success of low-energy internal cardioversion of AF.[41,42] Having completed preclinical testing, the device is now commercially available, and there is world-wide experience with about 180 implants. The treatment appears safe, effective and reliable, but clearly the treatment is only delivered after AF has begun. The device is therefore most suitable for patients with frequently recurrent persistent AF, but those paroxysmal AF suffers who have long duration AF episodes are also appropriate. The tolerability of internal shocks was an early concern, but is not proving a clinical problem. Atrial defibrillation has also been incorporated into conventional ventricular ICD's, and data are awaited.

CONCLUSION

Whilst much has been learnt both about the pathophysiology of paroxysmal AF and its treatment, current advice is based upon clinical data that are generally poor quality, and even at times anecdotal. This advice is summarised as follows:

1. Paroxysmal AF is a distressing but seldom life-threatening condition. Patients often harbour anxiety that their condition is serious, and allaying those fears forms an important treatment. Such reassurance alone may suffice for those who are not highly symptomatic and where there is not evidence that the condition is worsening. *Level of evidence - IV*
2. Complete suppression, reduction in episode frequency and early restoration of sinus rhythm improves long-term outcome by reducing the probability of permanent AF. *Level of evidence - IV*
3. Pharmacological therapy reduces the frequency of symptomatic paroxysmal AF episodes. The level of evidence for efficacy of individual agents is as follows:
    i Flecainide, propafenone, sotalol, disopyramide, quinidine. *Level of evidence - Ib*
    ii Amiodarone, beta blockers. *Level of evidence - IIa*
    iii Agents with no documented efficacy for paroxysmal AF include other antiarrhythmic agents (procainamide, mexilitine, morazicine), calcium channel antagonists and digoxin. *Level of evidence - IV*
    iv Symptoms during attacks may be attenuated, and possibly dangerous one-to one conduction of atrial flutter prevented by co-administration of effective AV blocking agents (verapamil, diltiazem and beta blockers). Agents with lesser or questionable efficacy in this role include digoxin, amiodarone and propafenone. *Level of evidence - IV*
4. Use of antiarrhythmic agents is only safe if due regard is given to co-existent cardiac conditions, and relative and absolute contraindications respected. Indiscriminate use of antiarrhythmic drugs increases mortality. *Level of evidence - III*
5. In highly symptomatic patients with paroxysmal AF, AV nodal ablation with implantation of a mode-switching dual chamber pacemaker reduces symptoms and

improves quality of life. *Level of evidence - IIa*

6. In highly symptomatic patients with paroxysmal AF, alternative non-pharmacological strategies (high rate atrial pacing, dual/novel site pacing, focal ablation, radio frequency MAZE procedures, surgical MAZE procedures) are beneficial in some subgroups. *Level of evidence - IIa*
7. In highly symptomatic patients with long duration episodes of paroxysmal AF, the implantable atrial defibrillator is effective, tolerable and safe. *Level of evidence - IV*

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