PAPER: RECENT DEVELOPMENTS IN THE MANAGEMENT OF ATRIAL FIBRILLATION

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Atrial fibrillation (AF) is the most common cardiac arrhythmia to trouble both patients and physicians;[1] it is often difficult to treat and is associated with significant mortality, morbidity and healthcare expenditure.[2,3] It is generally classified as either *paroxysmal*, where the episode terminates spontaneously, *persistent*, where cardioversion (electrical or pharmacological) is required for termination, or *chronic*, where cardioversion is unsuccessful (or not indicated) usually when the arrhythmia is long-standing.[4] The management of AF is divided into two strategies, partly determined by the above clinical classification. The aim may be to terminate paroxysms or persistent AF and maintain sinus rhythm (SR) (the so-called 'rhythm control' approach), or control the ventricular rate during paroxysmal, persistent or chronic AF (the so-called 'rate control' approach) along with a reduction in the thromboembolic risk inherent in the condition.

The management of AF is thus complex, and numerous guidelines have been published.[4,5] This article does not attempt to summarise these guidelines but recent developments mandate an overview of some of the advances in the management of this common arrhythmia.

'RATE' VERSUS 'RHYTHM' CONTROL

Atrial fibrillation alone carries a twofold increased mortality risk[6,7] and it was assumed that maintenance of SR would reduce this risk. Thus until recently it had been accepted that the primary goal in AF management was to maintain SR if possible. However, two clinical trials from either side of the Atlantic published last year have called this strategy into question. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial investigators[8] randomised 4,060 patients (mean age 70 years) in the US with AF and a high risk of stroke to either rate control with standard therapies, such as beta blockers or digoxin, or rhythm control using aggressive measures including repeated direct current cardioversion (DCCV) in combination with potent anti-arrhythmic drugs such as amiodarone. Patients were followed-up for a mean of 3·5 years. Attempted rhythm control offered no survival advantage (or disadvantage) with more adverse effects and hospital admissions in that group. In the Netherlands, the Rate Control vs Rhythm Control for Persistent Atrial Fibrillation (RACE) study[9] randomised 522 patients (mean age 68 years) with AF after their first DCCV to either rate or rhythm control. Patients were followed-up for a mean of 2·3 years and again rhythm control provided no mortality or morbidity benefits compared to rate control. The conclusion of both these studies was that pharmacological rate control and long-term anti-coagulation is at least as effective as (attempting) maintenance of SR in patients with persistent AF. These findings, however, will apply mainly to older patients with persistent AF and minimal symptoms; obviously a group of patients will remain who require an aggressive strategy to maintain SR for symptomatic or other reasons.

ANTI-COAGULATION

Atrial fibrillation is the strongest independent risk factor for embolic stroke.[6] Megatrials have convincingly established the benefits of anti-coagulation with oral warfarin in the prevention of thrombo-embolic stroke in patients with all categories of AF.[10,11] Warfarin confers a 62% relative risk reduction and guidelines recommend anti-coagulation in patients over 75 with chronic AF or under 75 with one or more risk factors such as hypertension or cardiac failure (Table 1). If a patient with persistent AF undergoes cardioversion authoritative guidelines[4,5] recommend that warfarin is continued for at least four weeks after (as well as three weeks before) SR is restored as the risk of thrombo-embolism persists during this period due to atrial stunning. However, in the previously discussed AFFIRM trial the greatest number of strokes occurred in patients who had discontinued their warfarin. It may be preferable to continue warfarin for longer periods in patients who have an increased risk of reverting to AF or have ongoing paroxysms of AF. For this reason some patients should remain on warfarin for longer periods, however, the optimum time duration is as yet undetermined. Future guidelines are likely to clarify this in view of the AFFIRM trial results. Aspirin therapy has proven inferior to warfarin in reducing risk and use is restricted to younger patients with AF who are at relatively low risk.

Patients who are most deserving of anti-coagulation are those where warfarin is under prescribed.[12] A number of reasons for this exist relating to genuine concerns of compliance, risk of life-threatening haemorrhage and lack of appropriate monitoring facilities. A recent retrospective analysis of 42,451 patients receiving anti-coagulation for any reason showed significant increase in mortality when the international normalised ratio (INR) was poorly controlled and determined that the optimum INR was 2·2–2·3; when patients' INR rose above 3·5 patient mortality rose significantly.[13]

TABLE 1

Annual risk of stroke on no treatment, aspirin, or warfarin in high, moderate and low risk patients with non-valvular AF.

Risk group	Untreated	Aspirin	Warfarin	NNT*
Very high Previous ischaemic stroke or TIA	12%	10%	5%	13
High Age over 65 and one other risk factor: • Hypertension • Diabetes mellitus • Heart failure • Left ventricle dysfunction	5–8%	4–6%	2–3%	22–47
Moderate • Age over 65, no other risk factors • Age under 65, other risk factors	3–5%	2–4%	1–2%	47–83
Low Age under 65, no other risk factors	1·2%	1%	c. 0·5%	200

* Number needed to treat with warfarin instead of aspirin for one year to prevent one stroke
(Adapted with permision from the Royal College of Physicians of Edinburgh Atrial Fibrillation Consensus Statement[5])

An exciting new development is suggested by the promising results of an oral direct thrombin inhibitor, ximelagatran, which inhibits the final step in the coagulation process. Unlike warfarin, ximelagatran has consistent pharmacokinetics and pharmacodynamics making dose titration and monitoring unnecessary. In the SPORTIF II study,[14] ximelagatran was shown to be safe and well-tolerated when used in 254 patients with non-valvular AF. In the recently published SPORTIF III study[15] a total of 3,407 patients (mean age 70 years) were randomised in an open-label fashion to a fixed dose of ximelagatran or adjusted-dose warfarin with a target INR of 2–3. Patients were followed-up for a mean of 17·4 months (4,941 patient years). There were no significant differences in thrombo-embolic events between warfarin and ximelagatran with less minor bleeding in the ximelagatran group. One concern, however, was the occurrence of significantly more episodes of deranged liver function tests in the ximelagatran group.

DIRECT CURRENT CARDIOVERSION

Direct current cardioversion (DCCV) has been used to terminate AF for over 40 years.[16] Traditionally the waveform used to deliver the shock has been monophasic. In recent years defibrillators have been developed that deliver the shock using a biphasic waveform where the direction of current flow is reversed during delivery. Studies have shown that biphasic defibrillation results in a higher initial cardioversion success rate with lower energy in patients with persistent AF.[17, 18] Biphasic shocks have also been shown to be more effective in patients with ventricular dysrhythmias and hospitals should now be switching to biphasic defibrillators. Cardioversion via internal transvenous atrial defibrillation has been shown to be effective in cardioverting patients with persistent AF refractory to external DCCV, although trials comparing this modality with biphasic external defibrillation have not been reported. Internal atrial defibrillation via an automatic implantable defibrillator is safe and has an 80% success rate. Atrial defibrillators are available in combination with implantable ventricular defibrillators, however, stand-alone devices have been developed.[19, 20] Potentially these devices could be implanted in selected patients. If patients developed AF they could attend either the pacing clinic to undergo internal atrial defibrillation or receive a shock at a convenient time in the community, programmable by the patient or their partner. The drawbacks appear to be mild discomfort from the shock and early recurrence of AF. Given the relatively benign nature of AF in the majority of patients, it seems unlikely that such devices will gain widespread utilisation, given the other therapeutic options available.

PHARMACOLOGICAL CARDIOVERSION AND MAINTENANCE OF SINUS RHYTHM

A number of established agents have been used to cardiovert patients to SR or maintain SR in those with paroxysmal or persistent AF, including sotalol, flecainide, amiodarone and propafenone. Of these amiodarone has been shown to be the most effective. In the CTAF study,[20] amiodarone demonstrated superior efficacy compared to sotalol or propafenone although 18% of patients had adverse effects secondary to amiodarone. In a sub-group analysis of the AFFIRM study,[21] the effectiveness of specific anti-arrhythmic drugs was assessed. Amiodarone was more effective at maintaining SR than either sotalol or class I agents (i.e. sodium channel blockers such as procainamide, disopyramide,

quinidine or moricizine). With serial therapy nearly 80% of patients were in SR at one year.

Dofetilide is an anti-arrhythmic drug available in the US but not the UK. It is a pure class III agent (i.e. prolongs action potential by increasing repolarisation and refractoriness) that has shown promising acute cardioversion rates[22, 23] and potential use for long-term maintenance of SR. It has been shown to be well tolerated and can be used in patients with left ventricular dysfunction. Azimilide is a similar agent with class III activity currently undergoing evaluation.

NON-PHARMACOLOGICAL STRATEGIES FOR THE MAINTENANCE OF SINUS RHYTHM

Despite the widespread use of drugs in patients with recurrent episodes of AF, the overall results are disappointing. Even using amiodarone which is recognised as the best therapy, only 65% of patients remain in SR in the long term and up to 20% of patients have significant side-effects from treatment.[20] If patients are significantly symptomatic and AF proves difficult to control with drug therapy a number of options exist to help maintain SR.

Pacing for atrial fibrillation

A significant percentage of patients with sinus node disease develop AF, and several prospective randomised trials have shown a reduction in the incidence of AF when patients are treated with atrial-based pacing systems rather then ventricular pacing for symptomatic bradycardia.[24, 25] A large US study randomised 2,010 patients with sinus node disease to either dual chamber pacing or ventricular pacing alone.[26] Although there was no significant mortality benefit, dual chamber pacing resulted in a significant reduction in the incidence of AF.

Atrial pacing at a high heart rate, in the absence of any conventional bradycardic indication, was initially employed to try to prevent persistent AF in patients with paroxysmal AF (PAF) but initial results were disappointing. More recently devices with advanced 'pace prevention' algorithms have emerged with more promising results. Pacemakers designed to deliver a high percentage of atrial paced beats, whilst maintaining the diurnal variation in heart rate, have been developed and are commercially available. The systems increase the atrial rate whenever a native rhythm emerges and periodically reduces the rate to search for intrinsic atrial activity. A recent trial designed to assess the efficacy of atrial 'overdrive' pacing using this algorithm, randomised 318 patients with AF and sick sinus syndrome to either rate responsive dual chamber pacing (DDDR) alone or DDDR pacing in combination with the atrial overdrive algorithm.[27] Symptomatic AF was significantly reduced in the group randomised to atrial overdrive pacing, although the absolute difference was small (2·5% in the control group compared to 1·87% in the atrial overdrive group). Some pacing devices incorporate other algorithms that can theoretically reduce the incidence of AF, for example 'post-ectopic rate smoothing' and 'post-mode switch high rate pacing', but their role in this context is as yet unproven. At the present time the implantation of these sophisticated pacemakers with one or more 'anti-AF' algorithms should probably be restricted to those patients who have conventional indications for pacing as well as troublesome AF, e.g. patients with sinus node disease, patients in whom anti-arrhythmic drug therapy produces unacceptable bradycardia or patients in whom total atrioventricular (AV) node ablation is anticipated and who therefore require pacemaker implantation anyway as a 'stepping stone' to the procedure.

Dual-site atrial pacing results in more homogenous depolarisation and repolarisation of the atria and may therefore theoretically reduce the tendency for AF to develop. Various techniques have been advocated mainly involving high right atrial pacing along with other sites such as the coronary sinus or interatrial septum in order to achieve earlier atrial activation. As yet there is no definitive evidence to encourage the general use of multi-site atrial pacing in the prevention of AF.

Interrogation of atrial electrograms stored by pacemakers has demonstrated that many episodes of AF occur in the context of other atrial arrhythmias such as atrial tachycardia and/or atrial flutter,[28, 29] with one study demonstrating that up to half of patients with PAF had organised atrial tachyarrhythmia preceding or occurring in addition to their AF. Treatment of these more organised rhythms with anti-tachycardia pacing may therefore reduce atrial tachyarrhythmia burden, one pacemaker at least is able to deliver rapid bursts of atrial pacing at a rate faster than the tachycardia and thus hopefully 'overdrive' the patient back into SR. Early studies using this form of overdrive pacing have been promising showing significant termination of atrial tachyarrhythmia with anti-tachycardia pacing[30, 31] and a reduction in arrhythmia burden (Figure 1).

Surgery

In 1987 Cox *et al.* demonstrated that a number of intra-atrial incisions could be performed intra-operatively to form anatomical barriers which reduced the number of circulating wavelets that cause AF.[32] Since then the so-called 'Maze procedure' has been refined and can now be used when patients undergo either a coronary artery bypass graft or valvular surgery. Results indicate 74–90% of patients remain in SR at three years with up to 6% of patients requiring a permanent pacemaker post procedure. Recently intra-operative cryoablation (and radiofrequency ablation) to the posterior left atrium around the four pulmonary veins has been used, however, only 69% of patients maintained SR at one year.[33] Attempts to replicate the Maze procedure using

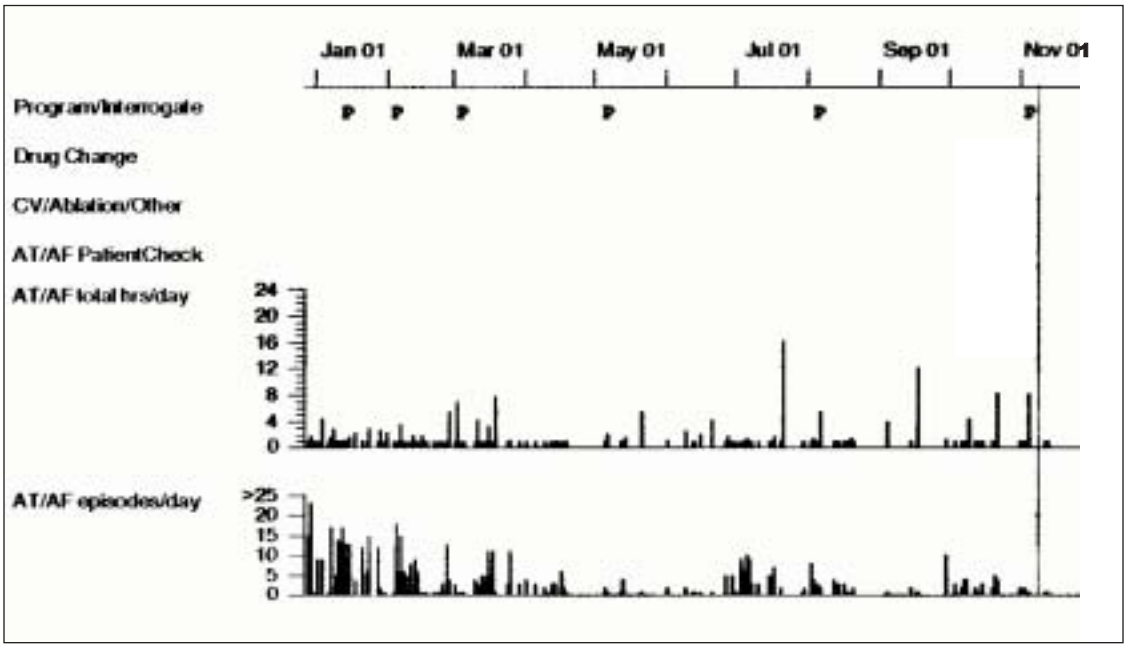

FIGURE 1

Part of the diagnostic log over a ten-month period of a pacemaker with several 'anti-AF' algorithms potentially programmable ('P'). The patient has PAF and intermittent complete heart block. Following implantation at the end of December 2000, an initial period of monitoring (in addition to dual chamber pacing) revealed frequent, daily bursts of AF. Progressive programming of various 'anti-AF' algorithms and anti-tachycardia pacing demonstrated a clear reduction in the burden of AF, as judged by the average number and duration of episodes per day.

percutaneous ablation techniques have been disappointing, with long procedure time and difficulties in achieving complete conduction block.

Radio frequency ablation

Interrupting conduction through the AV node and implanting a dual or single chamber pacemaker is a very effective method of controlling refractory symptomatic AF due to a poorly controlled ventricular rate. Success rates are >95% but there is a small risk, particularly of sudden death, probably due to ventricular tachyarrhythmias occurring in the first few months following ablation,[34] though this is probably minimised by appropriate programming of the pacemaker. Importantly the atria continue to fibrillate therefore anti-coagulation usually needs to be continued following the procedure.

An exciting new development has stemmed from the recent discovery that AF is often initiated by rapidly firing atria foci (or tachycardia), which usually originate in the pulmonary veins (Figure 2).[35] Attempts have been made to localise the origin of these foci in the pulmonary veins and successfully ablate them. Early success rates were modest and the procedure was not without complication, particularly pulmonary vein stenosis. The limitations of focal ablation have led to a technique which isolates the pulmonary veins by ablating the electrical connection at their ostia. This has shown higher success rates and is proving a more promising technique with success rates of up to 90% when combined with previously ineffective medical therapy. In a recently published study,[36] 589 patients with chronic AF were randomised to circumferential pulmonary vein ablation (using a sophisticated mapping system) compared to 582 patients who received anti-arrhythmic medication. Ablated patients showed significant survival benefits ($p<0{\cdot}001$) and improved quality of life compared to patients who received medical therapy. Recurrence of AF was much lower in the ablated group at one year (20% vs 58%). The emergence and refinement of pulmonary vein ablation may call for further evaluation of the best treatment for AF and large studies similar to AFFIRM and RACE may be required which include patients treated with curative radiofrequency ablation techniques.

CONCLUSION

The management of AF has progressed significantly over the past five to ten years. It is now acceptable to manage asymptomatic older patients (over 65 years) with pharmacological rate control and long-term anti-coagulation if at risk of thromboembolism. For patients who do not tolerate AF or in whom maintenance of SR is particularly desirable, a number of therapies are available, including class I or III anti-arrhythmic drugs, permanent pacemaker implantation (in selected cases), radiofrequency ablation of the AV node (with pacemaker implantation), and 'curative' ablation of the ostia of the pulmonary veins or ectopic foci shown to initiate AF.

The treatment of AF is constantly changing and this review only summarises a few of the major advances.

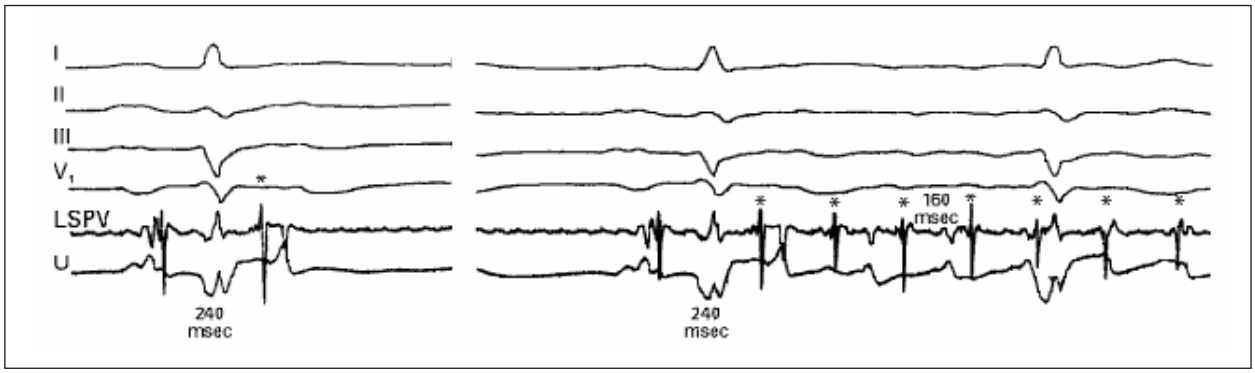

FIGURE 2

Onset of human AF from a focus in a left superior pulmonary vein (LSPV). The upper four tracings represent surface ECG leads with 'U', a unipolar signal from within the left atrium. The LSPV electrogram reflects local electrical activity in that pulmonary vein and is recorded by an electrode placed therein. The electrogram with the pulmonary-vein spike is the terminal part of a two-component electrogram obtained during SR. On the left, a sinus beat (with a terminal spike) was followed by an isolated atrial ectopic beat (asterisk) at a coupling interval of 240 msec. The electrogram of the ectopic beat characteristically shows temporal reversal, with the rapid deflection spike preceding the lower-amplitude, slower far-field atrial activity; the initiating spike suggests that the LSPV is the source of the ectopic beat. On the right, in the same patient, a train of spike discharges (asterisks) at a cycle length of 160 msec sets off AF. The spike discharges are also characterised by temporal reversal but exhibit a progressively prolonged conduction time to the atria. The coupling interval of the first spike on the right (240 msec) is identical to that of the isolated ectopic beat on the left. The surface ECG leads show corresponding AF. (Haissaguerre M *et al.,* 1998.[35] Copyright © 1998 Massachusetts Medical Society. All rights reserved. Reproduced with permission from the *New England Journal of Medicin*e.)

General practitioners, physicians and even general cardiologists cannot be expected to keep track of these advances but should be aware of the basic principles in managing AF and the indications for referral to an electrophysiologist in selected cases.

SUMMARY

- AF is the most common significant cardiac arrhythmia.
- In older patients with minimal symptoms rate control and long-term anti-coagulation may be as effective as attempts at rhythm control.
- Newer direct thrombin inhibitors that do not require dose titration or monitoring may replace oral warfarin in the next few years.
- For patients in whom AF is not tolerated or maintenance of SR is considered particularly desirable, a number of approaches should generally be considered:
    - Prophylactic anti-arrhythmic drug therapy.
    - Dual chamber pacing +/- various anti-AF pacing algorithms for those patients with an additional conventional indication for pacemaker implantation.
    - Radio frequency ablation of the AV node and pacing for drug resistant patients.
    - Surgical Maze procedure, or ablation, for patients undergoing concomitant cardiac surgery where the surgeon is trained in the procedure.
    - Radiofrequency ablation of the ostium of the pulmonary veins (or other ectopic foci shown to initiate AF).

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