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New Approaches to Atrial Fibrillation Management

A Critical Review of a Rapidly Evolving Field

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia, the prevalence of which is increasing with the aging of the population. Because of its clinical importance and the lack of highly satisfactory management approaches, AF is the

subject of active clinical and research efforts. This paper reviews recent and on-going developments in pharmacological and non-drug management of AF.

The ideal therapeutic goal for AF is the production and maintenance of sinus rhythm. Comparative studies suggest that available class I and III drugs have comparable and modest efficacy for sinus rhythm maintenance. Amiodarone, with actions of all antiarrhythmic classes, has recently been shown to have clearly superior efficacy compared with other available drugs. Newer agents are in development, but their advantages are as yet unclear and appear limited. A potentially interesting approach is the prescription of drugs upon the occurrence of an attack, rather than on a continuous basis. Recent insights into AF mechanisms may permit therapy to prevent development of the AF substrate.

An alternative to sinus rhythm maintenance is a rate control approach, with no attempt to prevent AF. Drugs to effect rate control include digitalis, β-blockers and calcium channel antagonists. Digitalis has limited value for control of exercise heart rate and for paroxysmal AF, but is particularly well suited for patients with concomitant AF and congestive heart failure. AV-nodal ablation and pacing is an effective alternative for rate control but leaves the patient pacemaker dependent. The relative merits of rate versus rhythm control are being evaluated in ongoing trials, preliminary results of which indicate no statistically significant differences in primary endpoints but highlight the risks of rhythm control therapy.

In patients requiring pacemakers, physiological pacing (dual chamber devices or atrial pacing) has an advantage over purely ventricular pacemakers in AF prevention. Newer pacing modalities that produce more synchronised atrial activation, as well as pacemakers that prevent excessive atrial rate swings, show promise in AF prevention and may soon see wider use. The usefulness of automatic atrial defibrillators is presently limited by discomfort during shocks.

Targeted destruction of pulmonary vein foci by radiofrequency catheter ablation suppresses paroxysmal AF. Efficacy in persistent AF is lower and still under study. Problems include potential recurrence in other veins and a small but nontrivial risk of pulmonary vein stenosis. Surgical division of the atria into zones with limited electrical connection, the MAZE procedure, is highly effective in AF prevention but is a major intervention that is not applicable to most patients.

In conclusion, significant advances are being made in the management of patients with AF but much more work remains to be done.

1. Epidemiology and Objectives of Therapy

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of 2% in the general population, and accounts for over 5% of hospital admissions for cardiovascular diseases.[1,2] AF can occur in the absence of other detectable heart disease, a form called 'lone' or 'idiopathic' AF, but is often associated with one or more of a variety of common cardiac conditions, including congestive heart failure (CHF), valvular heart disease, coronary artery disease, thyrotoxicosis and hypertension. Aging is a particularly important risk factor, with the incidence of AF rising to ~10% in octogenarians.[2]

Adverse consequences of AF derive from the loss of fine control of heart rate normally provided by autonomic regulation of the sinoatrial node pacemaker,[3] from a thromboembolic diathesis resulting from blood stasis in the fibrillating atrium,[4] and from the loss of the haemodynamic contribution of atrial contraction.[5] AF is the single most important contributor to stroke in the population over 75 years of age.[6] AF impairs quality of life[7] and may increase mortality, particularly

in patients with CHF.[8] The evaluation of AF management must also consider the various forms of AF and the overall clinical context. Paroxysmal AF involves self-terminating episodes that may be rare or extremely frequent, with durations that may vary from seconds to days, many of which may be asymptomatic. Persistent AF lasts indefinitely until terminated by medical intervention. When persistent AF cannot be successfully cardioverted, or cardioversion is judged to be not indicated, AF is termed 'permanent'.

The objectives of AF therapy are to reduce symptoms (e.g. palpitations, chest discomfort, tiredness, dyspnea and limited physical endurance), to prevent thromboembolic complications, and to eliminate detrimental effects on cardiac performance and longevity. AF therapy is suboptimal, and is an area of rapid investigation and innovation.[9] A detailed overview of antiarrhythmic drug therapy of AF appeared in *Drugs* in 1994,[10] and an overview of contemporary therapeutic practice was published recently.[11] This paper reviews emerging developments in AF treatment, and evaluates the impact on present and future management of the arrhythmia.

2. Drug Therapy for Maintenance of Sinus Rhythm

Restoration and maintenance of sinus rhythm should prevent AF-related adverse effects; however, without antiarrhythmic drugs, only ~25% of patients cardioverted from persistent AF will maintain sinus rhythm for up to 1 year.[12,13] Approximately 50% of recurrences occur within the first week after cardioversion and 90% by 6 months.[13,14] With antiarrhythmic drugs, sinus rhythm may be maintained in 50 to 65% of patients.[14-19] The major concern with antiarrhythmic drugs is the risk of proarrhythmia and mortality promotion.[10,20]

2.1 Restoration of Sinus Rhythm

The introduction of QRS-synchronised cardioversion with a monophasic waveform greatly improved the ability of physicians to restore sinus rhythm to patients with AF.[21] In a recent detailed study, electrical cardioversion was less likely to succeed for AF of longer duration, patients of greater weight and in the presence of idiopathic dilated cardiomyopathy.[22] Age, sex and the presence of hypertension, coronary artery disease or valvular heart disease were not predictive. Internal cardioversion (i.e. with the use of an intracardiac electrode catheter) may restore sinus rhythm to patients with AF who are refractory to external cardioversion.[23] However, with the demonstration that adjunctive antiarrhythmic drug therapy promotes sinus rhythm restoration by external cardioversion,[24] and the observation that cardioversion with biphasic waveforms is more effective than with monophasic waveforms,[25] the potential need for internal cardioversion has greatly decreased. Failure of cardioversion may be due to failure to terminate AF or to re-initiation of AF soon after rhythm normalisation (sometimes called 'early re-initiation of AF' or ERAF). ERAF can be prevented by antiarrhythmic drug therapy prior to electrical cardioversion.[26,27]

Conversion of AF to sinus rhythm can also be achieved by antiarrhythmic drugs. A wide variety of trials have been performed to evaluate many drugs for this indication. For details, the reader is referred to a recent, very thorough analysis of 88 studies.[28] All antiarrhythmic drugs are substantially more effective in terminating recent-onset (<7 days) AF. Conversion rates of recent-onset AF are in the range of 40 to 80% for intravenous procainamide, propafenone, flecainide and high-dose (>1.4g) amiodarone. Comparable results are achieved with oral quinidine, disopyramide, propafenone, flecainide and amiodarone at effective doses. Conversion by amiodarone is significantly slower than with the other compounds, and class III agents such as sotalol, dofetilide and ibutilide are somewhat less effective. The usefulness of drug termination must be considered in the context of the high spontaneous conversion rates of recent-onset AF (can be over 70% at 24 hours),[29] as well as in the face of the greater effectiveness of electrical cardioversion. Pharmacological conversion

rates are substantially lower in AF of longer duration, and the usefulness of pharmacological cardioversion in AF of longer standing is limited. The main roles of antiarrhythmic drugs for AF cardioversion are for recent-onset AF when electrical cardioversion is not readily available or has to be delayed, and as an adjunct to increase the effectiveness of electrical cardioversion.

2.2 Comparative Studies of Existing Agents for Maintenance of Sinus Rhythm

Virtually all class IA, IC and III antiarrhythmic agents have been found effective in maintaining sinus rhythm. A number of comparative trials have sought to determine relative effectiveness. Flecainide has been found equal in efficacy to quinidine and better tolerated.[30] In a controlled comparison with quinidine, propafenone was more effective in suppressing attacks and alleviating symptoms of paroxysmal AF.[31] On the other hand, comparisons of oral propafenone with sotalol have demonstrated either equal efficacy[32,33] or an advantage in favour of sotalol.[34] Sotalol has been found to be equally effective as quinidine in maintaining sinus rhythm and more effective in controlling the ventricular response rate during AF recurrences.[16] A recent study suggested that sotalol may be more advantageous in patients cardioverted from recent-onset AF (≤72 hours) [sinus rhythm at 6 months maintained in 93 *vs* 64%, p = 0.01], whereas quinidine was more beneficial in AF of longer duration (68 *vs* 33%, $p < 0.05$).[35] The possibility that specific populations of patients with AF might benefit more from specific classes of drugs is an interesting one for which there is experimental support[36] and merits further investigation.

Rates of maintenance of sinus rhythm with a variety of class I and III antiarrhythmic agents are ~50%. Amiodarone has actions of all antiarrhythmic drug classes.[10] Several non-randomised or small-scale studies of amiodarone provided sinus rhythm maintenance rates of 53 to 80%, suggesting superior efficacy in AF.[37-47] A meta-analysis comparing six trials of amiodarone 200 to 400mg

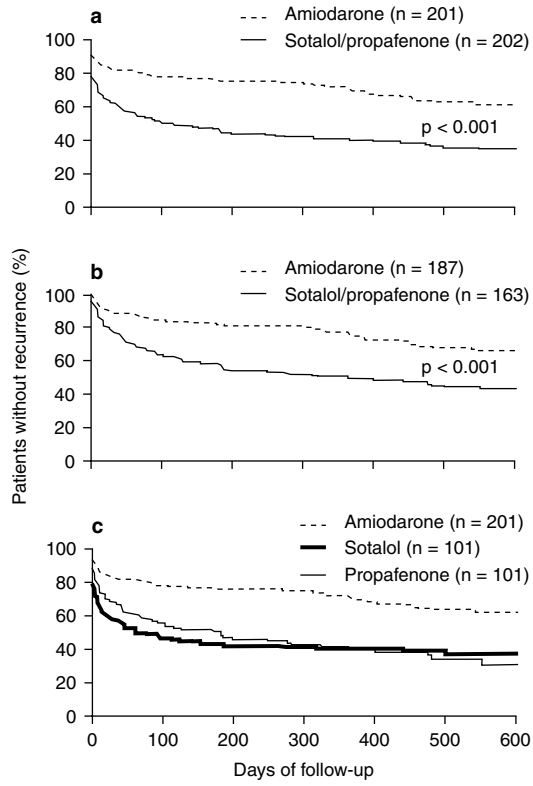

Fig. 1. Kaplan-Meier estimates of percentage of patients free of atrial fibrillation (AF) recurrence from the Canadian Trial of Atrial Fibrillation (CTAF). (**a**) Proportion of patients free of AF recurrence in the study groups (hazard ratio for recurrence in amiodarone group, 0.43 [95% CI: 0.32-0.57]). (**b**) Estimates for patients (amiodarone = 187; sotalol/propafenone = 163) who were in sinus rhythm 21 days post-randomisation. (**c**) Recurrence rates for patients who received amiodarone *vs* those randomised to sotalol and those taking propafenone. (Reproduced with permission from Roy et al.[15] Copyright© 2000. Massachussetts Medical Society. All rights reserved.)

(n = 315) with two trials of flecainide (n = 163) found amiodarone more effective and equally well tolerated.[48] In a randomised trial of 70 patients with recurrent symptomatic AF and >40% left ventricular (LV) ejection fraction, 25/35 (71%) patients receiving amiodarone 200 mg/day remained in sinus rhythm over 12 months compared with 14/35 (40%) patients receiving sotalol 80 to 360mg twice daily as tolerated (p = 0.008).[49]

The Canadian Trial of Atrial Fibrillation (CTAF) was the first large-scale prospective randomised trial of AF therapy[50] comparing low dose amiodarone 200 mg/day (n = 201) antiarrhythmic therapy with sotalol (n = 101) or propafenone (n = 101). CTAF provided compelling evidence of the superiority of amiodarone in maintaining sinus rhythm over sotalol and propafenone, which were found to be equivalent (figure 1).[15] Similar results were subsequently reported in a study of 186 patients with recurrent symptomatic AF randomised to amiodarone (n = 65), sotalol (n = 61) or placebo (n = 60).[51]

Overall, comparative studies suggest approximately similar and modest efficacy among propafenone, flecainide, sotalol and quinidine. Amiodarone is clearly more effective. Amiodarone appears somewhat less well tolerated but has fewer potentially serious pro-arrhythmic complications.[10]

2.3 New Antiarrhythmic Agents

2.3.1 Dofetilide

Dofetilide is a pure class III antiarrhythmic agent approved in 1999 by the US Food and Drug Administration for the treatment of AF and atrial flutter. It selectively inhibits the rapid component of the delayed rectifier K^+-current (I_{Kr}),[52,53] thus prolonging action potential duration, increasing refractoriness and suppressing re-entry.[54] The pharmacology of dofetilide has recently been extensively reviewed in *Drugs*[55] and a brief summary is provided in table I. Dofetilide is devoid of negative inotropic effects[56] and, possibly because of increased Ca^{2+}-entry during the prolonged action potential plateau,[57,58] increases atrial contractility post-cardioversion.[59]

Similar to several other class III agents, the action potential prolonging action of dofetilide may be lessened at higher frequencies and increased at lower frequencies. This 'reverse use-dependence' may limit efficacy in arrhythmia termination and increase pro-arrhythmic risks because of excessive repolarisation delay at low frequencies.[60-62] Dofetilide can terminate AF but has modest efficacy,[56,63-66] possibly because of reduced actions at the rapid rates of the fibrillating atrium.[62] Consistent with this notion, dofetilide is more effective in converting atrial flutter than AF.[63] Torsades de pointes arrhythmias occur after dofetilide-induced

Table I. Pharmacodynamic and electrophysiological properties of oral dofetilide and azimilide

Property	Dofetilide	Azimilide
Bioavailability (%)	>90	≈100
Time to peak plasma concentration (h)	2-3 in fasting state 3-4h with food	5.2-7.2
Concentration-response relationship	Linear	Linear
Plasma half-life (h)	6.2-9.7	78.8-96
Percentage protein bound	65	94
Time to steady state (twice daily dosing)	3d	3d
Clearance	Renal	Hepatic ≈90%, renal ≈10%
Active metabolites	None	One with class III activity (concentration <5% of parent drug)
Possible drug interactions	Cimetidine, verapamil, ketoconazole	No clinically significant effects
Ion channel blockade	I_{Kr}	I_{Ks}, I_{Kr}
Action potential duration	Prolongs	Prolongs
Effective refractory period	Prolongs	Prolongs
PR, QRS intervals	No effect	No effect
QT interval	Dose related prolongation	Dose related prolongation
Reverse use dependence	Moderate	Rate independent *in vivo*

I_{Kr} = delayed rectifier K^+-current; I_{Ks} = slower component of delayed rectifier current.

conversion to sinus rhythm in 3 to 8% of patients.[56,63,64]

Four multicentre, randomised trials have confirmed the safety and efficacy of oral dofetilide in maintaining sinus rhythm (table II).[67-71] The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) and European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide (EMERALD) studies evaluated the efficacy of dofetilide at three dose levels for patients with a recent history of persistent AF.[67,68] The highest dose of dofetilide 500μg twice daily increased the proportion of patients maintaining sinus rhythm ~2- to 3-fold over placebo. The Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) Study Group conducted two studies to evaluate the effects of dofetilide on mortality in patients with LV dysfunction, one in patients with CHF[69] and the other in patients post-myocardial infarction (MI).[70] Careful precautions were taken, including dose adjustment for renal failure and in-hospital initiation of therapy, to minimise the likelihood of torsades de pointes in this high-risk population.[72,73] Overall mortality was unaltered,[69,70] showing that in contrast to the negative impact produced by the class III agent d-sotalol (dexsotalol) in the Survival With Oral d-Sotalol (SWORD) study,[74] dofetilide can be used safely in this population with appropriate precautions. Beneficial effects for AF were manifest as both a greater conversion rate to sinus rhythm and a higher proportion of patients maintaining sinus rhythm. The EMERALD study showed a dose-dependent improvement in quality of life with dofetilide.[68] However, the risk of torsades de pointes, a potentially life-threatening arrhythmia, requires the drug to be used carefully and, in combination with a recommendation for in-hospital initiation, has greatly limited use to date.

2.3.2 Azimilide

Azimilide is a novel class III antiarrhythmic compound with the capacity to block both I_{Kr} and the slower component (I_{Ks}) of delayed rectifier current.[75-77] Blocking I_{Ks} has been suggested to produce a more favourable rate-dependent profile of action potential prolongation, with less attenuation of effects at rapid rates and less exaggeration at slow rates.[75,78] *In vivo* experimentation does suggest a favourable rate-dependent profile of the class III action of azimilide;[62,79] however, studies in ventricular myocytes have shown reverse use-dependent properties.[77] In addition to K^+-channel blocking actions, azimilide is also a weak blocker

Table II. Randomised, placebo-controlled trials of oral dofetilide in patients with atrial fibrillation (AF)

Design/parameters	EMERALD	SAFIRE-D	DIAMOND-MI	DIAMOND-CHF
Number of patients	671	325	1510	1518
Treatment arms	Dofetilide 125μg or 500μg bid, dl-sotalol 80mg bid, or placebo	Dofetilide125, 250, 500μg bid or placebo	Dofetilide 500μg bid *vs* placebo	Dofetilide 500μg bid *vs* placebo
Minimum follow-up	12m	12m	12m	12m
Underlying pathology	Sustained AF/AFL (>1wk <2y)	AF/AFL (≥2wk ≤6m)	LV dysfunction, <7d post-MI	LV dysfunction, (NYHA III-IV)
Primary end-point	Maintenance of sinus rhythm	Maintenance of sinus rhythm	All-cause mortality	All-cause mortality
Maintenance of sinus rhythm: dofetilide (highest dose) *vs* placebo	66% *vs* 21% at 12m	58% *vs* 25% at 12m	Restoration of sinus rhythm: 42 *vs* 12.5%	79% *vs* 42% at 12m
p-value	0.001	0.001	0.002	<0.001
Incidence of TdP	0.8%	0.8%	0.9%	3.3%

AFL = atrial flutter; **bid** = twice daily; **CHF** = congestive heart failure; **DIAMOND** = Danish Investigations of Arrhythmia and Mortality on Dofetilide; **EMERALD** = European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide; **LV** = left ventricular; **MI** = myocardial infarction; **NYHA** = New York Heart Association; **SAFIRE-D** = Symptomatic Atrial Fibrillation Investigative Research on Dofetilide; **TdP** = torsades de pointes.

of Ca^{2+}- and Na^{+}-channels,[76,77] providing a spectrum of action in some ways similar to amiodarone. The pharmacokinetics and principle pharmacodynamic properties of azimilide are summarised in table I. For details, the reader is referred to a recent thorough review.[80]

Potential clinical advantages of azimilide include excellent tolerability, a long half-life allowing once-daily dose administration and predictable pharmacokinetics, relatively unaffected by renal disease. Unlike dofetilide, clinical trials of azimilide have used simple, largely single dose administration regimens, and have not required in-patient initiation.[81,82] Efficacy against AF has been mixed in various trials, although a meta-analysis suggests significant efficacy.[81] Results of the azimilide post-infarct survival evaluation (ALIVE) trial, a large, double-blind, post-MI study comparing azimilide with placebo,[82] were presented at the 2001 Scientific Sessions of the American Heart Association, Anaheim, CA, USA. Mortality was virtually identical for placebo and azimilide groups. Patients in AF treated with azimilide were more likely to convert to sinus rhythm than placebo recipients and the incidence of torsades de pointes was low (<0.5%). The only significant adverse effect was idiosyncratic, self-limited neutropenia. Thus, azimilide shows promise and will be a useful contribution to therapeutic options for AF if clinical trials presently underway confirm its efficacy.

2.3.3 Other Drugs in Development

A number of additional drugs are presently in development. Tedisamil is a class III agent with bradycardic and anti-anginal properties,[83] with efficacy against AF. Dronedarone is an amiodarone derivative devoid of the iodine moiety, without the thyroid interactions that complicate amiodarone use.[84] Results of basic electrophysiological studies have been variable, one suggesting comparable pharmacological actions to amiodarone[85] and another suggesting much weaker actions.[86] Another compound in development is an anti-serotonin agent with apparently atrial-selective refractoriness prolonging actions and some efficacy in experimental AF.[87]

2.4 Novel Approach: 'Pill in the Pocket'

An evolving concept in AF therapeutics with great potential appeal has been deemed the 'pill in the pocket' approach. This concept is based on a number of well established principles: (i) many patients with AF experience infrequent recurrences (one to several times a year); (ii) recent-onset AF is much more sensitive to drug-induced termination than arrhythmias of longer duration;[88] and (iii) the risk of adverse drug effects is related to the duration of exposure.

Several studies have evaluated the efficacy and safety of conversion of recent-onset AF with oral doses of propafenone[89-94] and flecainide.[91,93] Single doses of propafenone 600mg and flecainide 300mg appear to have equivalent efficacy, typically resulting in sinus rhythm in ~70 to 80% of patients at 8 hours, which is significantly greater than placebo conversion rates of ~20 to 30%. Oral amiodarone 30 mg/kg also appears effective, but acts more slowly than flecainide or propafenone.[94,95] Of note, all of these studies have been performed in hospitalised patients. These data have led to the approach of avoiding continuous antiarrhythmic drug therapy for AF prophylaxis in patients with infrequent episodes, but rather providing a limited number of flecainide or propafenone tablets to take should AF occur and fail to resolve within a reasonable period, for example 1 hour. This method has considerable appeal, but the relative risks and effectiveness of the patient self-administered 'pill in the pocket' have yet to be established in a prospective clinical trial. Of particular concern with the class IC agents (propafenone and flecainide) is the risk of atrial flutter with 1 **:** 1 conduction, which can be quite dangerous.

2.5 The Role of Atrial Remodelling

A tremendous amount has been learned over the past 10 years about the pathophysiology of AF.[3] One of the most important discoveries has been

that atrial tachycardias like AF produce changes in atrial electrophysiology that make the atria more vulnerable to AF.[96] Decreases in atrial refractoriness caused by downregulation of L-type Ca^{2+}-current appear central to the promotion of atrial reentry and AF caused by atrial tachycardia.[97] There is evidence for a role of cellular Ca^{2+}-loading in the induction of atrial tachycardia induced remodelling.[98] Retrospective studies[99] and experimental data[100] suggested possible protection by the L-type calcium channel antagonist verapamil and led to clinical trials. Although one study showed potential benefit of verapamil against AF recurrence post-cardioversion,[101] another very well-designed study did not,[102] and subsequent experimental studies have failed to show benefit of L-type calcium channel antagonists against remodelling due to >24-hour atrial tachycardia.[103,104]

The prevention of tachycardia remodelling remains an attractive goal for which there is presently no demonstrated effective medical approach.

Another paradigm of AF-promoting atrial remodelling, characterised by interstitial fibrosis that interferes with atrial conduction, is caused by experimental CHF and resembles clinical pathology in AF.[105] This form of remodelling is in part prevented by ACE inhibition,[106] possibly accounting for AF prevention by ACE inhibitors in patients with post-MI LV dysfunction.[107]

2.6 Summary

Currently available drug options for maintenance of sinus rhythm are suboptimal. Conventional class IA and III agents have similar and modest efficacy, and significant pro-arrhythmic risks. Amiodarone is the most effective drug available and the least prone to produce ventricular proarrhythmia, but the potential for significant adverse effects and slow reversibility as a result of extensive tissue accumulation limit its use. Drugs in development have potential but limited advantages. The use of drug therapy only after the onset of an episode ('pill in the pocket') is an attractive option, particularly for the large number of patients with AF who have infrequent recurrences, but has yet to be studied in an outpatient setting. The prevention of AF-promoting remodelling is an attractive target for medical therapy that is still in its infancy. The improvement of pharmacological options for maintenance of sinus rhythm remains a major, largely unmet, need.

3. Control of the Ventricular Response

Many clinical manifestations of AF are determined by the ventricular response rate. Control of ventricular rate is therefore an important part of AF management, both for patients awaiting cardioversion and for those in whom maintenance of sinus rhythm is judged impossible or undesirable. The optimal rate control criteria in AF remain poorly defined.[108] Resting heart rates <80 to 90 beats per minute (bpm) and exercise heart rates <110 to 120 bpm are usually sought. In relatively healthy individuals, this target exercise heart rate may be insufficient and limit physical capacity. Excessively rapid ventricular response rates can themselves cause CHF.[109] It is presently unknown whether ventricular function is adversely affected by a heart rate response that averages <100 bpm but is nonetheless greater than would be maintained in sinus rhythm.

3.1 Advantages and Disadvantages of a Rate Control Strategy

Controversy exists as to whether maintenance of sinus rhythm should be the primary goal of AF therapy ('rhythm control strategy') or whether patients should be left in AF with adequate rate control ('rate control strategy'). Potential advantages of rate control include: (i) symptomatic improvement is achieved in most patients; (ii) the drugs used do not produce ventricular proarrhythmia; (iii) drugs used for rate control are less costly; and (iv) a highly effective non-pharmacological therapy (AV nodal ablation/permanent pacemaker) exists. Disadvantages of the rate control strategy are: (i) AF persists, causing atrial remodelling with risk of permanent AF; (ii) loss of atrial contraction, particularly detrimental to CHF patients; and (iii)

rhythm control may be more effective for controlling symptoms and preventing stroke.

Differences in mortality between rhythm control and rate control strategies have been evaluated in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial,[110] publication of which is expected in the near future. Preliminary results of the AFFIRM trial and of a Dutch multicenter study (RACE) comparing rate and rhythm control strategies were presented at the American College of Cardiology scientific sessions in March, 2002 in Atlanta, GA, USA. In the AFFIRM trial, there was no significant difference in mortality between the strategies but the mortality rate was marginally greater with rhythm control ($p \sim 0.06$). There was a nonsignificant excess of stroke and a significant increase in the incidence of torsades de pointes with rhythm control. In the RACE trial, there was no significant difference in the primary endpoint (cardiovascular death, heart failure hospitalisation, thromboembolic complications, severe bleeding and pacemaker implantation) between strategies.

These preliminary findings do not indicate clear superiority of one approach over the other, while highlighting some of the recognised risks of rhythm control. Further evaluation awaits publication of the complete results in the scientific literature. Rate and rhythm control produced similar overall symptomatic results in the recently published Pharmacological Intervention in Atrial Fibrillation (PIAF) trial,[111] but exercise tolerance was better with rhythm control. Rate control requires administration of anticoagulant therapy to prevent thromboembolic complications. Patients managed with a rhythm control strategy may also require anticoagulation before and after rhythm normalisation. The use of anticoagulation in AF is an important and complex subject, which space limitations do not permit us to discuss.

3.2 Drugs for Rate Control

Digitalis, the first drug used for rate control, remains a popular choice. Although digitalis slows the ventricular rate during AF at rest, it acts by vagal enhancement and provides poor rate control during daily activities and, in particular, exercise because of reduced vagal tone[108,112-114]. Digitalis fails to reduce the ventricular rate during AF paroxysms and may be associated with longer attacks.[115] Because of its positive inotropic action, digitalis is first-line treatment for rate control of patients with AF in CHF as a result of impaired systolic ventricular function.[116] Otherwise, it is used as a secondary or adjunct agent to β-blockers or calcium channel antagonists.

β-Blockers control the response rate at rest and during exercise;[117] however, they can produce chronotropic incompetence and thereby reduce exercise tolerance. It has been suggested that β-blockers, such as pindolol, with intrinsic sympathomimetic activity may produce rate control without concomitant bradycardia.[118] The practical utility of this approach is poorly documented. β-Blockers improve survival in patients with CHF and may be particularly useful in patients who have AF and CHF.[119-121] The L-type calcium channel antagonists verapamil and diltiazem are effective at controlling ventricular response and improving exercise performance in patients with AF.[122] Caution is needed in patients with CHF because calcium channel antagonists may adversely affect the prognosis,[123] either by virtue of neurohumoral enhancement or negative inotropic action. Amiodarone also slows the ventricular response to AF and may be a useful component of rate control therapy,[124] although its potential for serious long-term toxicity needs to be considered. A recent study comparing digoxin, atenolol, diltiazem, digoxin plus diltiazem and digoxin plus atenolol for rate control showed that digitalis and diltiazem alone were least effective and that digitalis plus atenolol produced the most effective rate control as assessed by exercise testing and ambulatory monitoring (figure 2).[108]

3.3 Non-Pharmacological Control of Ventricular Rate During Atrial Fibrillation (AF)

AV-nodal ablation (generally with permanent pacemaker implantation) is an alternative when

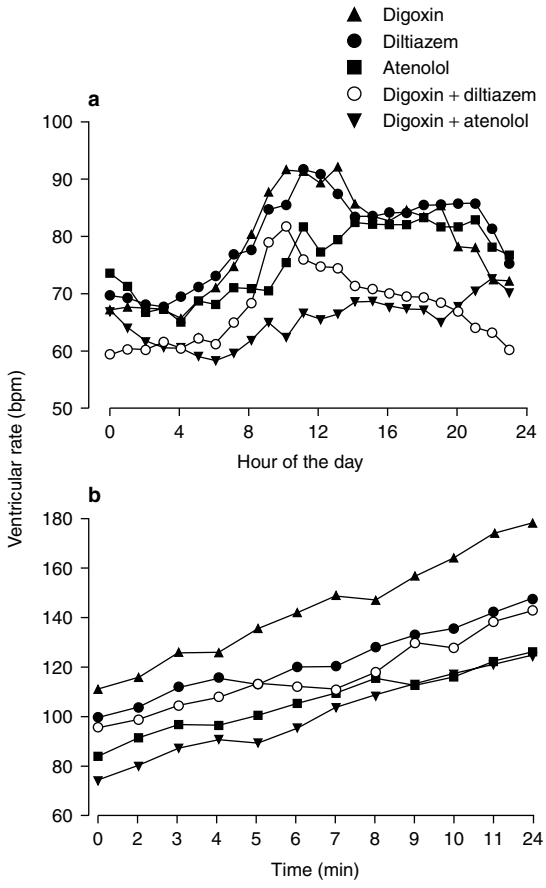

Fig. 2. Effects of various drugs on ventricular rate during atrial fibrillation over the course of a day (**a**) and during exercise (**b**) (reproduced with permission from Farshi et al.[108]). **bpm** = beats per minute.

adequate rate control cannot be achieved by drug therapy. Radiofrequency catheter ablation is the most commonly used technique and is presently the procedure of choice, but other methods have been used, including direct current shocks, intracoronary ethanol infusion, surgical cryoablation and catheter cryoablation.[125-129] AV-nodal ablation and pacing has good safety and provides effective rate control without drug therapy,[116,130-132] and is associated with improvement in quality of life, particularly in the most symptomatic patients (figure 3).[133-138]

The need for permanent pacing and a potential risk of malignant ventricular arrhythmias following ablation[139] led to some concerns about potential long-term negative survival effects. However, data have been published that largely dispel such concerns.[140] There is also a theoretical risk of deleterious effects on ventricular function of LV asynchrony due to ventricular pacing. Patients with paroxysmal AF handled by ablation and pacing have a substantial rate of progression to permanent AF.[141] Ablation techniques that modify AV conduction without inducing complete AV block have been described,[142] but two recent trials showed ablation to be a more effective treatment than AV node modification.[136,143]

3.4 Summary

Challenges to optimal rate control include a lack of empirically defined objective endpoints, the limited ability of pharmacological rate control to reproduce normal physiological heart rate adjustment, and limited efficacy in patients with paroxysmal AF. AV-nodal ablation and pacing can produce good results in symptomatic patients, but produce pacemaker-dependency and often leave the patient in permanent AF. Ongoing trials will provide more information about the relative merits of rate control versus rhythm control strategies.

4. Implantable Device Therapy

With advances in bioengineering, a variety of implantable devices have been applied to AF therapy. These range from simple pacemakers to devices incorporating a variety of sophisticated stimulation paradigms and atrial defibrillation.

4.1 Conventional Pacemaker Therapy

Ventricular pacing can lead to retrograde capture of the atria, which could theoretically result in atrial premature activation and the initiation of reentrant AF in the presence of a vulnerable substrate.[3] Early non-randomised studies suggested that physiological pacing (atrial/atrial-inhibited or dual-chamber pacing) in patients requiring pace-

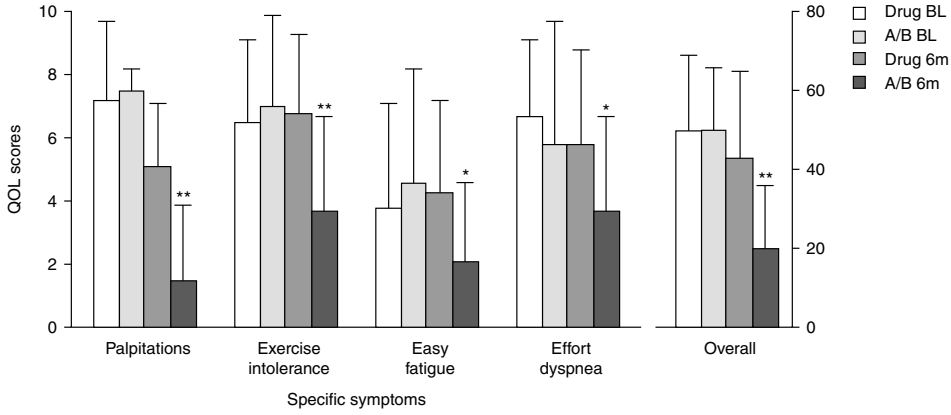

Fig. 3. Effects of ablation and pacing (A/B) versus rate control drugs (Drug) on quality of life (QOL) scores (mean ± SD) at pre-treatment baseline (BL) and at 6-month follow-up (6m) among patients with severely symptomatic paroxysmal atrial fibrillation (based on data in Brignole et al.[135]). Lower QOL scores = fewer symptoms. * $p < 0.05$; ** $p < 0.001$, *vs* BL.

makers for symptomatic bradycardia reduces the incidence of AF compared with ventricular (unichamber) pacing.[144-146] Subsequently, small randomised studies in patients with sick sinus syndrome arrived at the same conclusion.[147-149] Two large randomised trials of pacing mode have recently been reported. In 1474 patients with a conventional pacemaker indication but without persistent AF, physiological pacing significantly reduced the occurrence of AF by 18% (6.6% annual rate with ventricular pacing *vs* 5.3% with physiological pacing).[150] This beneficial effect increased progressively over 4 years after pacemaker implantation (figure 4), and was clearest in the most pacemaker-dependent patients.[150-152] These findings were confirmed in the recently reported Mode Selection Trial (MOST).[153]

Heart rate varies over the day and even normal individuals can experience periods of significant bradycardia. Bradycardia can increase the dispersion of refractoriness and promote re-entrant arrhythmias like AF, so it has been thought that conventional pacemaking to prevent bradycardia might help to prevent AF even in patients without symptomatic bradycardia *per se*. In the atrial pacing peri-ablation for prevention of atrial fibrillation trial (PA^3), 97 patients with paroxysmal AF intolerant or resistant to antiarrhythmic drug therapy received a dual-chamber (DDDR) pacemaker and were randomised to active therapy (demand pacing at 70 bpm) or no therapy (demand pacing at 30 bpm). Although premature atrial contractions were suppressed and bradycardia was eliminated in the active pacing arm, the AF recurrence rate was unaltered.[154,155]

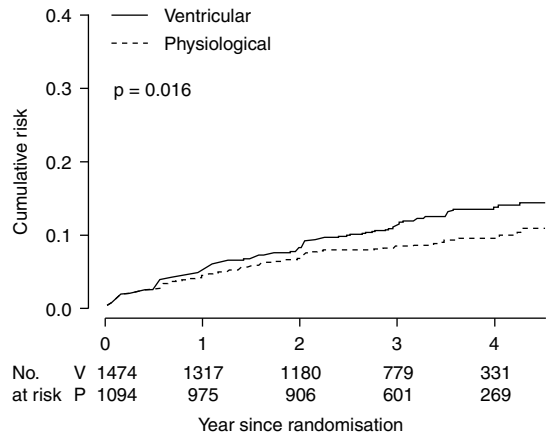

Fig. 4. Effects of physiological pacing (P) versus ventricular pacing (V) on atrial fibrillation recurrence (reproduced with permission from Skanes et al.[151]).

4.2 Multisite and Alternative-Site Pacing

Atrial conduction abnormalities play a significant role in the pathophysiology of the arrhythmia.[3] Pacing at multiple sites simultaneously and/or pacing at central sites, such as Bachmann's bundle or the interatrial septum, can produce more synchronous atrial activation, reduce refractoriness dispersion and potentially prevent atrial re-entry.[156] Alternative single-site right atrial pacing from Bachman's bundle, the interatrial septum and the coronary sinus ostium have been reported to prevent AF in several preliminary reports.[157-160] Long-term, randomised studies in larger groups of patients are needed before concluding that alternative-site pacing is effective and practical for prevention of AF.

Multisite atrial pacing has also been evaluated in a number of studies. Daubert et al. reported that simultaneous right and left atrial stimulation reduced the incidence of AF in a select group of patients with marked intra-atrial conduction delay.[161,162] Saksena's group subsequently reported that pacing from two right atrial sites (high atrium and atrial septum) in patients with bradycardia and AF prevents AF recurrence compared with single-site pacing.[163] Consistent dual-site atrial pacing delayed AF recurrences and lowered 'AF burden' (hours/day in AF) in 22 patients with paroxysmal AF and no bradycardic indication for pacing.[164] A recent larger study (Dual Site Atrial Pacing to Prevent Atrial Fibrillation, DAPPAF) randomised 118 patients with bradycardia and a history of AF to single-site pacing at 80 bpm, dual-site pacing at 80 bpm or demand pacing at 50 bpm.[165] Dual-site pacing was associated with fewer device-recorded atrial tachyarrhythmias. Leclerq et al.[166] recently observed an advantage of dual-site versus single-site pacing in patients with prolonged P waves (>120ms) but no difference in patients with shorter P waves. Therefore, dual-site pacing may be of particular value in those most likely to benefit, with evidence of substantial atrial conduction abnormalities, and differences in study populations may explain some of the discrepancies in the literature.

4.3 Pacing Algorithms for AF Therapy

Rather than simply pacing the atria at a fixed rate during bradycardia or pauses, new stimulation algorithms are designed to maintain atrial capture as much as possible and to smooth variations in atrial rhythm after premature contractions or after termination of an arrhythmia. The AF Prevention by Overdriving (PROVE) study showed a 34% reduction in the number of AF episodes and a 48% shortening of episode duration with the addition of an overdrive-pacing algorithm to conventional dual-chamber (DDDR) stimulation.[167] In another study, atrial-pacing algorithms reduced the mean number of AF episodes per day but did not reduce the total time spent in atrial arrhythmia.[168] An implantable ventricular cardioverter-defibrillator device incorporating atrial-pacing prevention and rapid-stimulation algorithms significantly reduced the time spent in AF among patients with ventricular tachyarrhythmias.[169]

4.4 Implantable Atrial Defibrillators

Given the enormous impact of ventricular defibrillators in therapy of malignant ventricular arrhythmias, the use of an atrial implantable defibrillator is an appealing strategy. Two devices have entered clinical trials and shown substantial efficacy in AF cardioversion.[170,171] Atrial defibrillators have been shown to reverse some of the consequences of atrial tachycardia remodelling (figure 5),[172] a scientifically interesting and potentially clinically valuable result. Unfortunately, the use of implantable atrial defibrillators has been greatly limited by the painful nature of cardioversion shocks, resulting in poor patient acceptance and limited applicability for cardioversion in the outpatient setting.[173] Further technical advances are likely to be needed before implantable atrial cardioverters can be applied more widely beyond the experimental stage.

4.5 Summary

Physiological pacemakers for bradycardia are associated with a lower recurrence rate of AF than

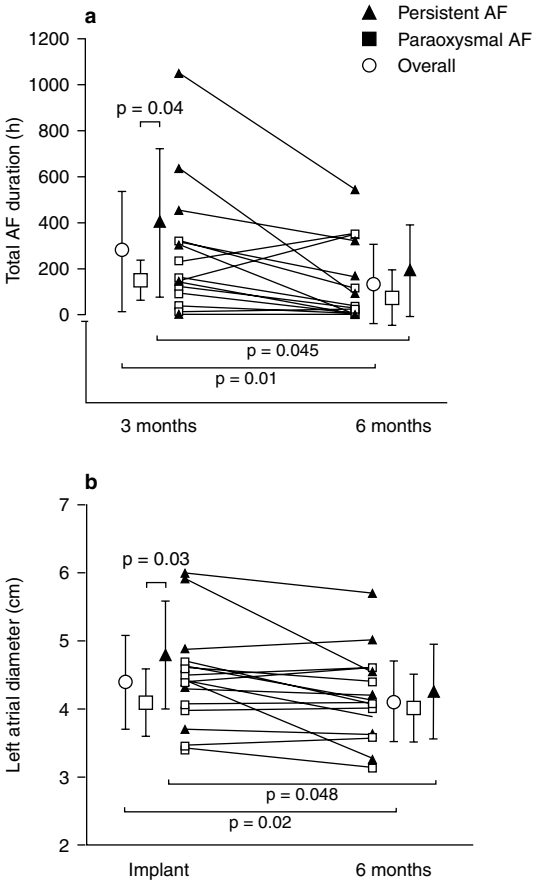

Fig. 5. Changes in atrial fibrillation (AF) duration (**a**) and left atrial diameter (**b**) following implantation of an atrial defibrillator. Results are shown for individual patients, as well as mean ± SD for persistent (triangles), paroxysmal (squares) and all (circles) patients (reproduced with permission from Tse et al.[172]).

single-chamber ventricular demand devices. Multisite pacing and pacing at sites intended to synchronise atrial activation may be useful in the prevention of AF but the results to date have been conflicting and the approach remains experimental. AF prevention algorithms have some utility in the prevention of AF and may eventually become an option for a larger number of patients at risk of AF requiring pacemakers for bradyarrhythmias. Implantable atrial cardioverters are successful in converting AF but their applicability is still greatly limited by shock discomfort and suboptimal outpatient applicability.

5. Ablation

Selective tissue destruction by catheter-based procedures has revolutionised the management of conditions, such as paroxysmal atrial tachycardia and atrial flutter. AF has been a more difficult challenge because of its complex pathophysiology; however, substantial progress has been made over recent years.

5.1 Catheter-Based Procedures Related to Surgical MAZE

The MAZE procedure was designed to divide the atria into relatively isolated tissue blocks in order to prevent the formation of the multiple reentry circuits deemed necessary to maintain the arrhythmia.[174] Its success led to great interest in developing a catheter-based equivalent.[175] Initial attempts involved the dragging of ablation catheters over the atrial endocardial surface in the hopes of containing continuous lines of block with multiple adjacent punctate lesions. Experimental studies highlighted the difficulty of obtaining continuous lines of block with this approach[176] and indicated the potential arrhythmogenicity of incomplete lesions.[177]

The initial clinical approach involved right atrial lesions only, since the right atrium is much easier to access percutaneously than the left. Right atrial lesions alone proved to be disappointing, with success rates as low as 33% despite continuing medical therapy in some patients.[178] The addition of left atrial lesions augmented the success rate,[179] but also resulted in more dangerous and longer procedures that were technically more difficult and more time consuming. Potentially serious complications included pericardial effusions, pulmonary embolus, inferior MI, transient ischaemic attack and thrombosis of the pulmonary veins, due in large measure to extensive charring of the endocardial surface.[180] In addition, procedural success remains incomplete, despite recent

improvements secondary to the introduction of electroanatomic mapping.[181,182]

Because of the risks, difficulty and incomplete success of the catheter-based MAZE, and the success of more limited procedures targeting the pulmonary veins, the latter have largely replaced the former at the moment.

5.2 Catheter-Based Procedures Targeting the Pulmonary Veins

In 1966, Nathan and Eliakim[183] noted that sleeves of atrial tissue surround the pulmonary veins for up to 5cm inside the vein wall, with sleeves tending to be longer in superior as opposed to inferior veins. A major advance occurred when Haïssaguerre et al.[184,185] demonstrated that in a majority of patients AF is initiated by extrasystolic triggers in the pulmonary veins, and that localisation and ablation of these triggers can cure AF. Since then, procedures for eliminating pulmonary vein sources have evolved considerably.

Initially, localising the targets for ablation proved difficult because of the complexity of navigating the posterior left atrium and pulmonary veins with their multiple branches. When atrial ectopy was infrequent, localising the site of origin at a 4 to 5cm distance within a pulmonary vein branch was an arduous task. In one study, as many as 32% of patients undergoing mapping for ectopic triggers failed to have ablations because there was insufficient atrial ectopy to localise arrhythmia origin.[186] In addition, some patients proved to have multiple arrhythmogenic sites,[187] and AF recurrences occurred because of emergence of a previously latent focus in a non-ablated vein. Electrocardiographic mapping of ectopic P wave morphology[188] and the use of multiple multipolar catheters[189] have been applied to define arrhythmogenic veins with greater precision.

Haïssaguerre et al.[190] recently developed an approach to pulmonary vein isolation based on electrical mapping within veins, achieving a 71% success rate. Pappone et al.[191,192] used electroanatomical mapping to create continuous lesions around pulmonary vein orifices, with a reported AF control rate of ~80%. Success was greater among patients with more extensive lesions (~32% of the left atrium), raising the question of whether a simple reduction in electrical mass might have contributed. A variety of new catheters and energy delivery systems have been developed specifically for pulmonary vein ablation,[193,194] but their specific advantages and utility remain to be established.

The most serious potential complication of pulmonary vein ablation is pulmonary vein stenosis, presenting with dyspnea and beginning up to 3 months after a procedure.[195-198] The incidence in larger series varies from 3 to 8%.[186,187] It is believed that limiting ablation energy and extent, and avoiding ablation beyond pulmonary vein ostia, help to minimise the risk of pulmonary vein stenosis.

5.3 'Hybrid' Approaches

Because of the limited efficacy of catheter-based ablation procedures for AF, interest has developed in 'hybrid' approaches that combine ablation procedures with drug therapy to maintain sinus rhythm.[199] Useful approaches may include the application of limited linear ablation procedures or pacing interventions along with drug therapy, the addition of rhythm control drugs rather than attempting a second ablation in patients with recurrence following pulmonary vein ablation, and the application of isthmus ablation to AF patients who develop typical atrial flutter while taking antiarrhythmic drugs.[199] It remains to be established whether such approaches have superior efficacy with acceptable risks, or whether they simply expose patients to potential adverse effects of multiple treatment modalities without a substantial improvement in symptomatology.

5.4 Surgical Procedures for AF

The first successful surgical procedure for AF, the 'corridor' procedure of Guiraudon,[200] isolated the sinus node, AV node and a connecting corridor from the rest of the atria. Ventricular rate was then governed by sinus node activity but the patient re-

mained in AF. The MAZE procedure of Cox followed[174] and has been by far the most successful non-pharmacological procedure for AF. A variety of refinements have been made as the MAZE procedure evolved over time.[201] Its greatest disadvantage is the requirement for extensive open-heart surgery, greatly limiting applicability to otherwise well patients with AF. The major role for the MAZE operation is in patients requiring concomitant open-heart procedures, such as mitral-valve replacement, as well as for a limited number of selected individuals with highly symptomatic AF refractory to other management.

5.5 Summary

The targeted destruction of cardiac tissues has revolutionised the management of a variety of cardiac arrhythmias but not as yet AF. Substantial progress has been made, with pulmonary vein ablation emerging as a fairly effective and safely used catheter-based procedure, and the surgical MAZE as a very effective but highly invasive surgical approach. At the moment, the application of these procedures is limited to selected patients in highly specialised centres.

6. Conclusions

Significant advances are being made in all areas of the management of patients with AF, including drug therapy to maintain sinus rhythm, rate control strategies, the use of implantable devices and ablation procedures. Nevertheless, the arrhythmia remains a significant challenge, reflecting its complex and multifactorial nature. It appears unlikely that any single innovation will constitute a sufficient breakthrough to revolutionise the management of AF. Sustained progress along a number of fronts will be needed to provide more effective and safer options for the management of AF across the broad segment of the population with AF.

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