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**Atrial Fibrillation in  
Hospital and General  
Practice: the Sir James  
Mackenzie Consensus  
Conference**

**Restoring Sinus Rhythm**

**Maintaining Sinus Rhythm**

**Preventing Thromboembolism**

**Optimal Cardiovascular Function**

**Final Consensus Statement**

**Guest Editor:  
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## EDITORIAL INTRODUCTION

In 1898, James Mackenzie, a general practitioner and cardiologist in Preston, described atrial fibrillation. The centenary of this description appeared an appropriate time to review the management of this common arrhythmia, which is increasingly prevalent in ageing societies and which can cause heart failure and thromboembolism (particularly stroke). While several recent studies have helped to clarify management, much controversy remains and the topic seemed appropriate for a two-day consensus conference according to the established Royal College of Physicians of Edinburgh methodology.

For the first time, the consensus conference was held outwith the College, in St. Andrews where Sir James Mackenzie established his medical research institute. The conference was held as a joint venture by the College and the University of St. Andrews on 3 and 4 September 1998. About 150 participants from both primary and secondary care attended, and after an excellent introductory historical lecture on Sir James Mackenzie by Dr David Sinclair, Pro-Dean of St. Andrews University Medical School, they were invited to consider four key questions set by the Organising Committee:-

- How do We Maintain Sinus Rhythm in Paroxysmal Atrial Fibrillation?
- How do We Restore Sinus Rhythm in Persistent Atrial Fibrillation?
- How do We Achieve Optimal Cardiovascular Function in Atrial Fibrillation?
- How do We Prevent Thromboembolism in Atrial Fibrillation?

Two days of presentations and lively debate later, the Consensus Panel, ably Chaired by Professor Kim Fox, produced a Consensus Statement which is published in this supplement, together with the background papers and the abstracts of the oral presentations.

Perceptions of management from primary care, cardiologists, geriatricians, neurologists and others were fully aired and discussed, and we hope that the Consensus Statement and its background papers will be useful in both development of local guidelines for management, and for the management of individual patients. The conference was certainly useful to the development group of the Scottish National Clinical Guideline on Antithrombotic Therapy during its final drafting (SIGN publication No. 36, available from the SIGN Secretariat at the College, or on the SIGN website: [www.show.scot.nhs.uk/sign/home/htm](http://www.show.scot.nhs.uk/sign/home/htm)).

We hope that Sir James Mackenzie would have approved of this Consensus Conference, which debated in his final workplace both the science and the art of management of this common cause of morbidity and mortality.

PROFESSOR S.M. COBBE  
PROFESSOR G.D.O LOWE

## FINAL CONSENSUS STATEMENT

Atrial fibrillation (AF) may be classified as paroxysmal, persistent (if it does not spontaneously terminate but reverts to sinus rhythm with electrical/pharmacological intervention), or permanent. This arrhythmia affects about 5% of the UK population over 65 years of age, with prevalence rising to 10% in those over 75.

AF is associated with valvular and ischaemic heart disease, heart failure, hypertension, and diabetes. It occurs with acute myocardial infarction, thyrotoxicosis, pulmonary embolism, toxins such as alcohol, acute respiratory infections, cardiac surgery, and chest injury and can develop whenever the left atrium is dilated. However, 50% of all patients with paroxysmal AF and 20% with persistent or permanent AF have otherwise normal hearts ('lone AF').

AF is not benign. It is a major cause of morbidity, and doubles mortality. Better treatment of AF could substantially reduce the burden of illness in society, especially through prevention of stroke.

The fast and irregular heart rate of AF can cause palpitations, dizziness, malaise, anxiety, and heart failure; but the most serious consequence is ischaemic stroke, due to embolism from the left atrium.

AF is found in 15% of all stroke patients and 2-8% of patients with transient cerebral ischaemia. The risk of ischaemic stroke in AF without rheumatic heart disease is about 5% per annum but varies according to the presence of specific factors in a given individual. After an initial embolism the stroke recurrence rate is 12% per year and the annual risk of death is 5%.

Optimal assessment of the patient with AF includes a full history and examination, a 12-lead electrocardiogram, an echocardiogram (to determine whether or not valvular disease and left ventricular systolic dysfunction are present), and other investigations to identify underlying causes and guide treatment.

The treatment of AF can be complex, and may include the use of potentially hazardous therapies; thus it requires close collaboration between the primary and secondary health care teams.

Here we review four questions related to control of symptoms and prevention of thromboembolism in non-rheumatic AF.

### HOW DO WE MAINTAIN SINUS RHYTHM IN PAROXYSMAL AF?

If a patient has 'lone AF' with infrequent attacks that are well tolerated, antiarrhythmic drug therapy is not indicated. When the symptoms are troublesome, either beta-blockers or class Ic antiarrhythmic drugs (e.g. flecainide, propafenone) should be used as first-line treatment. Class Ic antiarrhythmic drugs, sotalol, and amiodarone must only be started under hospital supervision. In cases where there is evidence of underlying heart disease such as hypertension or coronary disease, beta-blockers have particular advantages; but when heart failure is present, amiodarone is the drug of choice.

Digoxin is not effective since it does not prevent paroxysms or control the ventricular rate when they occur. There are electrophysiological interventions that may be helpful in patients whose symptoms do not respond to drug therapy.

### HOW DO WE RESTORE SINUS RHYTHM IN PERSISTENT ATRIAL FIBRILLATION?

A patient with very recent onset AF requires immediate assessment and treatment with heparin. Therapy to restore sinus rhythm is most successful when given early.

If it is certain that AF has been present for two days or less, cardioversion should be attempted electrically or pharmacologically. Warfarin therapy is not required in these patients if cardioversion is successful. Flecainide is the drug of choice in these circumstances provided that left ventricular systolic function is normal; in cases of impaired left ventricular function, amiodarone should be used.

If AF has been present for more than two days, electrical cardioversion should be employed because pharmacological cardioversion is less likely to succeed, and anticoagulation is essential. To reduce the risk of thromboembolism, warfarin should be given to achieve an international normalised ratio (INR) in the range 2.0-3.0 for three weeks before cardioversion and continued for at least four weeks after cardioversion. With this strategy the risk of thromboembolism early after the procedure is reduced from 5-7% to 1-2%. Whether warfarin should be given beyond four weeks is uncertain, but this treatment may be considered in patients with a continuing high risk of recurrence of AF (large left atrium, poor left ventricular function, hypertension) or previously symptomless AF.

If persistent AF is of less than three months' duration, we recommend an attempt at restoration of sinus rhythm. Cardioversion is especially appropriate where a precipitant has been corrected (e.g. a chest infection, thyrotoxicosis, alcohol binge) and the patient has a structurally normal heart.

In patients with AF persisting beyond three months or where the duration of AF is uncertain, it is unclear whether or not rhythm control (i.e. restoration of sinus rhythm and maintenance for as long as possible) is more effective than rate control combined with anticoagulation at reducing long-term morbidity and mortality. These approaches are being compared in three randomised trials, and at present the choice of treatment should be based on physician judgment and informed patient preference.

Electrical cardioversion is initially successful in three-quarters of patients but relapse is frequent (25-50% at one month and 70-90% at one year). Treatment with an antiarrhythmic drug before and after cardioversion can increase both the initial success rate and the proportion of patients maintaining sinus rhythm in the longer term (to 50-60% at one year). It is not certain which patients will benefit from this approach. Those most likely to require

antiarrhythmic therapy for maintenance of sinus rhythm are patients with longstanding AF, structural heart disease, and hypertension. We do not know for how long treatment should be continued after cardioversion or which drug or drug sequence is most effective; amiodarone is commonly used.

#### HOW DO WE ACHIEVE OPTIMAL CARDIOVASCULAR FUNCTION IN ATRIAL FIBRILLATION?

Haemodynamic impairment in AF results principally from the rapid ventricular response. Optimal cardiovascular function is best obtained by restoration and maintenance of normal sinus rhythm, but for many patients this is not achievable, and the goal of treatment is then to limit the ventricular rate to 90/minute at rest and 180/minute on exercise.

Digoxin alone may control the ventricular rate in a resting patient, but it is less effective at controlling the heart rate during exercise. Consequently, a beta-blocker (e.g. atenolol) or a rate-limiting calcium channel blocker (e.g. verapamil) should be considered as first-line treatment, particularly in patients with coexisting hypertension or coronary disease. In heart failure, digoxin remains the treatment of choice for rate control.

If monotherapy is ineffective then combination therapy should be considered (e.g. digoxin and beta-blocker, or digoxin and a rate-limiting calcium channel blocker). When verapamil is prescribed less digoxin is required. Beta-blockers should not be given in combination with verapamil.

For selected patients in whom medical therapy has failed or is not tolerated, electrophysiological interventions, such as radiofrequency ablation of the atrioventricular node together with implantation of a rate-responsive pacemaker, may be indicated.

#### HOW DO WE PREVENT THROMBOEMBOLISM IN ATRIAL FIBRILLATION?

The following comments apply to all forms of AF

Warfarin therapy decreases the risk of ischaemic stroke by about 65%, aspirin by only 20%. Warfarin and aspirin should only be given together in special circumstances.

Patients with high risk of ischaemic stroke (one or more of: previous stroke or transient cerebral ischaemia; >75 years of age; hypertension; diabetes mellitus; coronary artery disease; congestive heart failure; left ventricular dysfunction) should receive warfarin therapy unless it is contraindicated. Patients aged 65–75 years without other risk factors are at moderate risk and can be treated with warfarin or aspirin. Isolated left atrial enlargement is not an independent risk factor for thromboembolism.

In general, a target range of 2.0–3.0 for the INR gives satisfactory protection while minimising the risks of major haemorrhage. There is uncertainty about the safety of higher ratios in patients >75 years of age, for whom a target of 1.6–2.5 may represent a better balance between risk and benefit.

For patients at moderate or high risk of stroke in whom warfarin is contraindicated, aspirin should be prescribed. Contraindications to warfarin include risk of bleeding due to coexisting medical conditions, and any tendency to falls or other exposure to trauma. Another consideration is the likelihood of poor concordance (compliance), which will be influenced not only by the patient's ability to manage medications but also by local facilities for control of the

INR. Special care must be taken with other drugs that interact with warfarin, including amiodarone. Patient preference is important.

Low-risk patients with AF should be treated with aspirin 75 mg–300 mg.

Anticoagulant therapy after an acute cerebral ischaemic event should be delayed until most of the deficit has resolved or, in the case of more severe strokes, more than two weeks has elapsed.

#### COMMENTS

We have considered only the four questions we were asked to address. Detection and management of underlying conditions and associated risk factors are important.

Patient participation is integral to good management. Patients must be informed of the risks and benefits of any of the treatments offered, and also of alternatives that may be available locally or elsewhere.

Therapeutic decisions in AF should take into account the need to maximise health gains from limited resources by use of the most cost-effective therapies.

There are many remaining areas of uncertainty about the management of AF, especially in relation to the first three questions. There is more evidence on the fourth question, although elderly patients have been under-represented in clinical trials. Further research is essential.

## CONSENSUS PANEL

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<b>Professor Michael Steel</b>	School of Biological and Medical Science, University of St. Andrews.

## HOW DO WE MAINTAIN SINUS RHYTHM IN PAROXYSMAL ATRIAL FIBRILLATION?\*

J.E.P. Waktare,<sup>†</sup> A.J. Camm<sup>†</sup>

### INTRODUCTION

While the choice of appropriate treatment of all atrial fibrillation (AF) can be difficult, when the disorder occurs as self-terminating paroxysms some particular problems 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). Current drug therapy is limited by side-effects and incomplete efficacy, and persisting concerns regarding proarrhythmia. 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, the paroxysmal AF needs consideration for prophylactic antiarrhythmic drug therapy in the meantime. 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 can not 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 conclusions. 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, and may usefully be classified using the '3P' classification<sup>1,2</sup> for chronic AF (Figure 1). This divides the disorder into a paroxysmal form, where AF generally self terminates; a persistent form, where AF does not spontaneously convert but reverts readily to sinus rhythm with electrical or pharmacological cardioversion; and permanent AF, where cardioversion is not possible or the patient or doctor prefer to allow 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

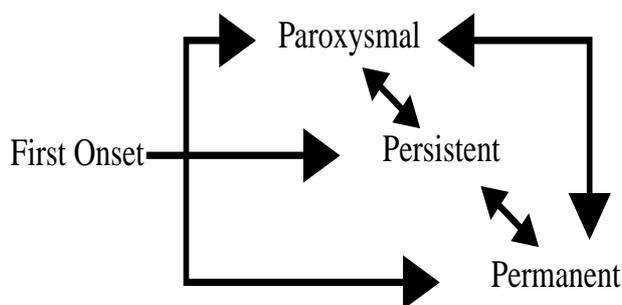


FIGURE 1

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 over time a patient may move between these types of AF.

ventricular rate and prevent thromboembolism. 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 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<sup>3</sup> or stroke.<sup>4</sup> 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 is derived from suppression of paroxysmal AF or from another mechanism is often unknown. In one of the few insights into this issue, Page *et al.*<sup>5</sup> showed that only approximately one in 12 episodes of paroxysmal AF was symptomatic. By contrast, episodes of paroxysmal supraventricular tachycardia were always symptomatic.

\*A background paper prepared for the Royal College of Physicians of Edinburgh Consensus Conference on Atrial Fibrillation in Hospital and General Practice.

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TABLE 1  
Mechanisms of reducing symptoms from Paroxysmal AF

Mechanism	Comment/Examples
Reduce frequency of paroxysmal AF	Presumed predominant mechanism of benefit of antiarrhythmic agents
Reduce duration of paroxysmal AF episodes	Possible secondary mechanism of benefit of antiarrhythmic agents
Reduce heart rate during episodes	Definite effect of beta blockers, verapamil, diltiazem and may occur with some other agents. Available evidence suggests that digoxin does not slow heart rate at onset of paroxysmal AF. <sup>26</sup>
Regularise rhythm during paroxysmal AF	Implantation of a dual chamber mode-switching pacemaker with AV nodal ablation works by providing a regular ventricular response at a physiologically appropriate rate. It is possible that some benefit of drugs is 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 to be related to peripheral vascular responses rather than tachycardia rate. <sup>27</sup> It is possible that modulating neurohumoral response may provide patient benefit.

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 thromboembolism and tachycardiomyopathy, are preventable with appropriate treatment, suitable screening and follow-up. Specific therapy may be unnecessary if attacks are infrequent, well tolerated, and short-lasting. However, if the frequency or duration of attacks increase, 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;<sup>6</sup> evidence that increasing duration of AF promotes atrial dilatation<sup>7</sup> which is known to predispose to AF;<sup>8</sup> and preliminary reports of increasing intervals between AF episodes following prompt cardioversion.<sup>9</sup>

PHARMACOLOGICAL METHODS

A wide range of drugs has been shown 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, thus hindering 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 and subjective, and that usually vary between trials.

Safety concerns in pharmacotherapy for AF have arisen from the increased mortality in those prescribed antiarrhythmic drugs in some<sup>10-12</sup> but not all<sup>13,14</sup> post-infarction trials. A meta-analysis of quinidine for AF patients suggested that this agent may be associated with an increased risk of death,<sup>15</sup> but other studies of patients with supraventricular arrhythmias are reassuring.<sup>16</sup> The overall impression is that with proper drug selection based on patient criteria (Table 3), antiarrhythmic therapy is safe as long as treatment is monitored with electrocardiography, serum electrolyte checks and other investigations as appropriate. A specific concern in this patient group 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 for 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, the resting ECG QT interval is monitored, and high doses or inappropriate drug combinations are avoided (e.g. co-administration of anti-histamines). Some groups are at particularly high risk of Torsades, like those with ventricular hypertrophy, and the arrhythmia is more common in young females.

Of the agents listed in Table 2, flecainide has the largest number of randomised and non-randomised studies in this field, is generally well tolerated 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 first-line. 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, amiodarone is only supported by uncontrolled studies but, despite this, is believed to be highly effective. It is usually recommended for second- or third-line use, although physicians increasingly use this therapy as the treatment of choice. It is proper to usually reserve it for those who fail other agents because of the drug’s numerous side-effects, most of which are minor (hypersensitivity to sunlight, sleep disturbance and benign corneal microdeposits) but some of which are potentially life-threatening (pulmonary fibrosis). It deserves early

TABLE 2  
Selected trials of drug therapy for paroxysmal AF\*

Trial drugs	Trial design	Efficacy†	Side-effects
Flecainide vs. Placebo <sup>28</sup>	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 <sup>29</sup>	Rand; Open, Crossover	100 % suppression in 50% of patients vs. 16-32% with quinidine.	Flecainide 0, Quinidine ++
Flecainide vs. Propafenone <sup>30</sup>	Rand; Open; Parallel	Proportion discontinuing therapy similar because of inadequate response: flec = 23%; propaf = 24%	Flecainide +, Propafenone ++
Propafenone vs Placebo <sup>31</sup>	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 <sup>32</sup>	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 <b>or</b> poor response) much higher on plac (45% vs. 14%)	Propaf ++
Propafenone vs. Quinidine <sup>33</sup>	Rand; Blind, Crossover	Proportion with > 75 % reduction in attacks: propaf = 87%; quinidine = 46%	Propaf +, Quinidine +
Propafenone vs. Sotalol <sup>34</sup>	Rand; Blind, Crossover	Proportion with > 75 % reduction in attacks: propaf = 79%; sotalol = 76%	Propaf +, Sotalol +
Propafenone vs. Sotalol <sup>35</sup>	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 +++ <sup>(‡)</sup>
Amiodarone <sup>36</sup>	Uncontrolled; Rx resist pt.	Effective in 9 of 13 patients who had failed at least two previous agents	Amiod ++

\*Due to 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);<sup>37</sup> Murgatroyd *et al.* (digoxin vs. placebo, atenolol vs. disopyramide vs. placebo);<sup>38,39</sup> Naccarelli *et al.* (flecainide vs. quinidine, findings similar to Van Wilk);<sup>29,40</sup> Pritchett *et al.* (propafenone vs. placebo);<sup>41</sup> Pietersen *et al.* (flecainide vs. placebo)<sup>42</sup>

**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

Side-effects: + = requiring discontinuation in 5-11%; ++ = 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.

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 clinician 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) 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.<sup>17</sup>

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 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.

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, Quinidine, and newer Class 3 agents	Left ventricular hypertrophy (e.g. hypertension), hypokalaemia and hypomagnesaemia (e.g. diuretic use), young females.
Symptomatic bradycardia and Stokes-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 of 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.

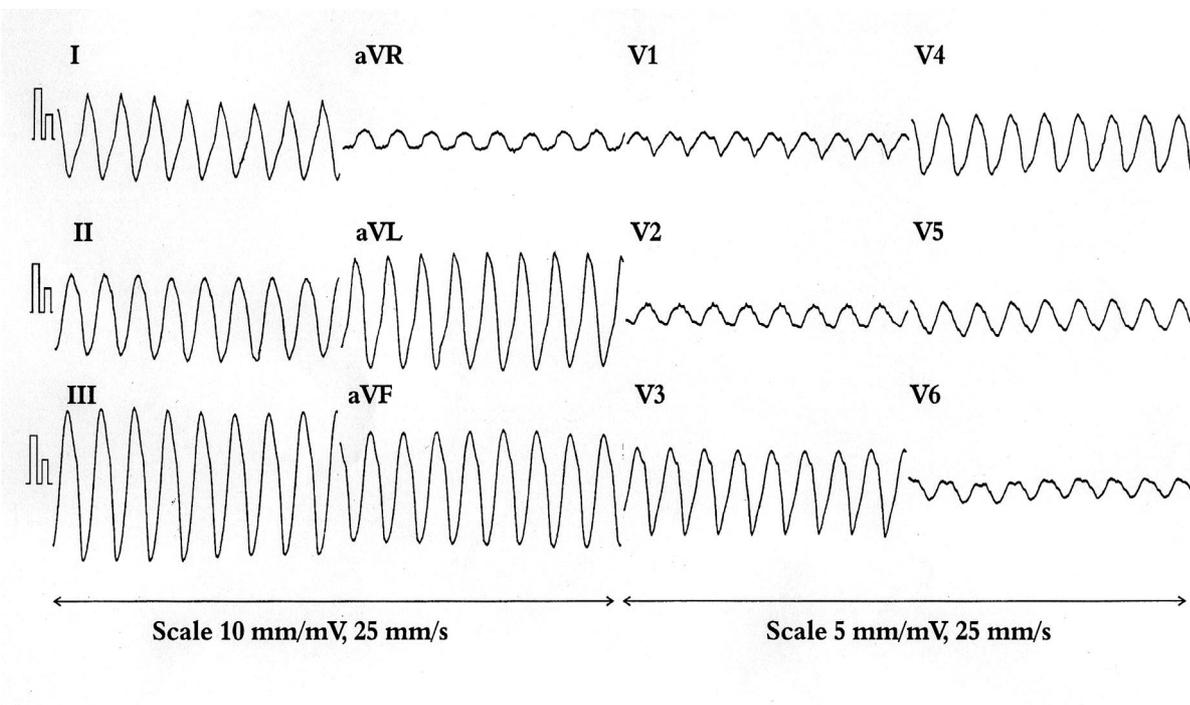


FIGURE 2

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.

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’.

The surgical maze procedure has been developed and refined over several years.<sup>18,19</sup> 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 and 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,<sup>20-22</sup> when the additional surgery is of little adverse consequence to the patient.

In patients with paroxysmal AF which is resistant to 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 patient pacemaker-dependent for life), failure of satisfactory symptomatic benefit in some, and increased likelihood of developing permanent AF,<sup>23</sup> with its attendant thromboembolic risk. 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, rapid ‘mode switching’ seems 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

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 the atrial by the pacemaker	<ul style="list-style-type: none"> <li>• Potentially preventative</li> </ul>	<ul style="list-style-type: none"> <li>• Unproven</li> <li>• Not effective for all</li> </ul>
Novel atrial pacing methods	Lead implanted at unusual sites or multiple leads to suppress AF	<ul style="list-style-type: none"> <li>• Potentially preventative</li> </ul>	<ul style="list-style-type: none"> <li>• Unproven</li> <li>• Complicated</li> <li>• Not effective for all</li> </ul>
Ablation of underlying focal atrial tachycardia	Case reports describing several patients in whom AF was initiated by an atrial tachycardia.	<ul style="list-style-type: none"> <li>• Potentially curative</li> </ul>	<ul style="list-style-type: none"> <li>• Uncertain how common this mechanism is</li> </ul>
Surgical MAZE procedure	See text	<ul style="list-style-type: none"> <li>• Potentially curative</li> <li>• Available</li> </ul>	<ul style="list-style-type: none"> <li>• Major surgery required</li> <li>• Post-procedure sinus node dysfunction</li> </ul>
Radiofrequency ablation MAZE procedure	Similar principle to surgical maze, but performed by creation of radiofrequency ablation lines	<ul style="list-style-type: none"> <li>• Potentially curative</li> </ul>	<ul style="list-style-type: none"> <li>• Long difficult radiofrequency ablation</li> <li>• Systemic thromboembolism and pulmonary venous obstruction</li> </ul>
AV nodal ablation with implantation of mode switching dual chamber pacemaker	See Figure 3	<ul style="list-style-type: none"> <li>• Effective</li> <li>• Available</li> </ul>	<ul style="list-style-type: none"> <li>• Does not maintain atrial function (risk of thromboembolism remains, and atrial transport lost during AF)</li> <li>• Renders patient pacemaker-dependent</li> </ul>
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	<ul style="list-style-type: none"> <li>• Effective</li> <li>• Available</li> </ul>	<ul style="list-style-type: none"> <li>• May not prevent AF episodes</li> <li>• Pain during defibrillation</li> </ul>

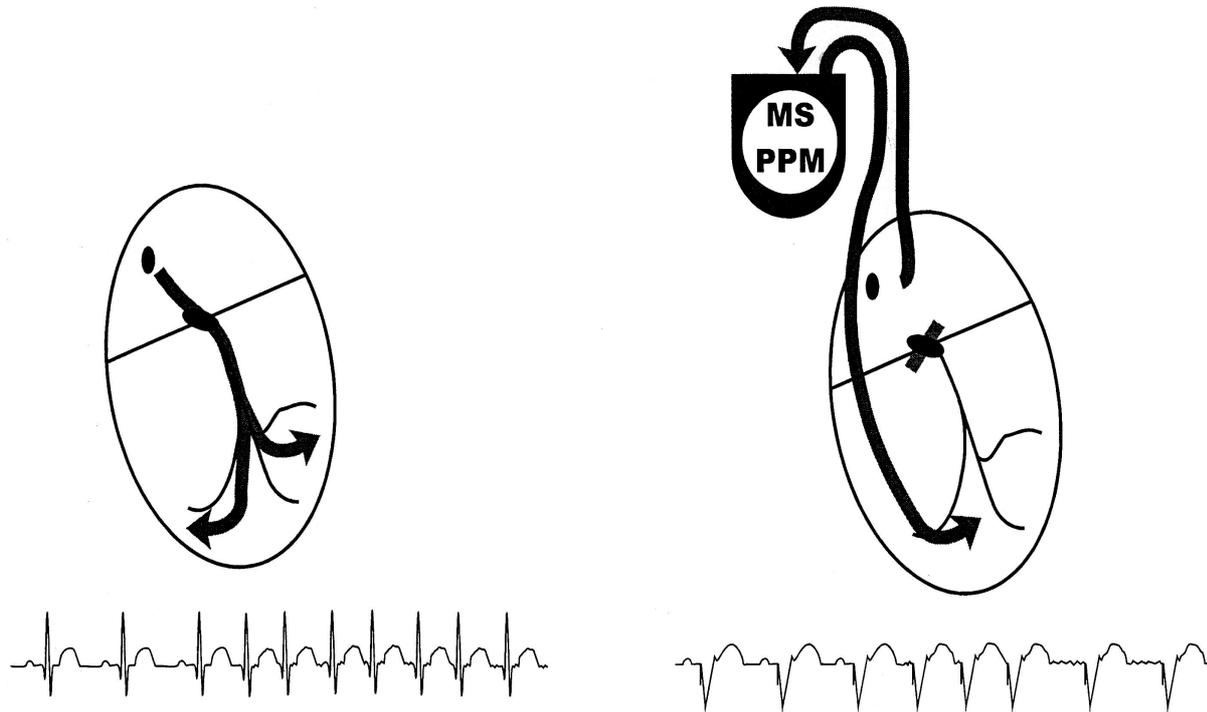


FIGURE 3

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-Purkinjee 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 at close to the pacemakers 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.

AF.<sup>24,25</sup> Having completed preclinical testing, the device is now commercially available, and there is worldwide 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 sufferers 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 ICDs, 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**

1. 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**
2. 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**
3. In highly symptomatic patients with paroxysmal AF, alternative non-pharmacological strategies (high-rate atrial pacing, dual/novel site pacing, focal ablation, radiofrequency MAZE procedures, surgical MAZE procedures) are beneficial in some subgroups. - **Level of evidence - IIa**.
4. In highly symptomatic patients with long duration episodes of paroxysmal AF, the implantable atrial defibrillator is effective, tolerable and safe. - **Level of evidence - IV**

#### ACKNOWLEDGEMENT

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ADDENDUM

*Non-pharmacological therapy - radiofrequency ablation of 'focal' AF*

Since the time of writing, there has been a major publication describing successful radiofrequency ablation of paroxysmal AF (Haissaguerre M., Jais P., Shah D.C. *et al.* Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins. *N Engl J Med* 1998; **339**:959-66.), and the subject has received considerable coverage in the popular press. The treatment holds the promise of complete cure of paroxysmal AF without need for long-term drug or implanted device therapy. To date extensive experience worldwide is limited to a single centre. It is therefore premature to speculate about the eventual usefulness of the technique, but this should become clearer in coming years.

## HOW DO WE RESTORE SINUS RHYTHM IN PERSISTENT ATRIAL FIBRILLATION?\*

J. R. Hampton†

### INTRODUCTION

While atrial fibrillation is an arrhythmia that is relatively easy to define and recognise, the underlying diseases that cause it are not. It is associated with advancing age, rheumatic and ischaemic heart disease, hypertension, and diabetes.<sup>1,2</sup> It can be caused by acute myocardial infarction, thyrotoxicosis, pulmonary embolism, poisons such as alcohol, acute respiratory infections, cardiac surgery, and chest injury. It can occur whenever the left atrium is dilated, as in dilated cardiomyopathy. And it can also occur in healthy people with apparently normal hearts, when it may be paroxysmal or permanent. Given the spectrum of underlying disease - or non-disease - it is hardly surprising that the evidence of efficacy of different ways of converting atrial fibrillation to sinus rhythm is not very good.

Apart from aetiology, atrial fibrillation is sometimes classified as paroxysmal, sustained (or persistent) and permanent. This classification is based on a self-fulfilling prophecy: if a patient reverts spontaneously he has paroxysmal fibrillation, if the rhythm can be converted it is sustained or persistent, and if it cannot be converted it is permanent. Paroxysms of atrial fibrillation can last anything from seconds to days. It is self-evident that trials of methods of conversion will be difficult: a patient with paroxysmal atrial fibrillation may convert spontaneously coincidentally with drug administration, and if treatment groups are unbalanced in the proportion of patients with atrial fibrillation that is actually paroxysmal, sustained (i.e. potentially convertible) or permanent (not convertible) treatment effects will be difficult to identify.

When atrial fibrillation seems likely to be self-limited (for example, in patients with acute myocardial infarction) control of the ventricular rate with digoxin, beta blockers, or verapamil may be all that is required. Nevertheless it is important to know how best to manage patients with atrial fibrillation for the arrhythmia has definite disadvantages, whatever the underlying cardiac disease. A patient with atrial fibrillation may be troubled by palpitations, and heart failure may develop simply because of an uncontrolled ventricular rate. Heart disease that is concealed so long as a patient remains in sinus rhythm may become apparent when atrial fibrillation occurs. Atrial fibrillation carries a risk of embolization, and if anticoagulants are used there will be a risk of bleeding. Conversely, conversion of atrial fibrillation to sinus rhythm improves exercise tolerance, left ventricular ejection fraction, and cardiac output.<sup>3</sup>

Historically conversion of atrial fibrillation was achieved with quinidine. This drug, which continued in widespread use in North America long after it had been abandoned in the UK, caused gastrointestinal upsets and it was associated with a phenomenon that used to be called 'quinidine syncope'. It was appreciated that it could cause sudden death, and older physicians will remember that a test dose of quinidine 3 grains before beginning 5 grains three times daily was considered wise - in fact quinidine 3 grains was referred to as 'the coroners dose' because it was believed that a coroner would accept sudden death due to quinidine as mischance provided that such a test dose had been used. The use of quinidine for the conversion of AF was overtaken by the development of the electrical 'cardioverter'.

### ELECTRICAL CARIOVERSION

The conversion of tachyarrhythmias to sinus rhythm by means of an electric shock was introduced by Lown.<sup>4</sup> He described the first patient treated, in 1961:

An elderly woman in the throes of acute myocardial infarction developed drug-refractory ventricular tachycardia, accompanied by hypotension and pulmonary oedema. Large doses of quinidine and procainamide slowed the ventricular rate but provoked profound shock. The patient kept on muttering, with adequate reason, that she was dying. A single 100 watt-second synchronised discharge resulted in prompt restoration of sinus rhythm, with immediate clearing of the pulmonary oedema and restoration of normal blood pressure. The patient exuded a sense of well-being; the only problem was to assure her that she was in the hospital recovery room, not in the hereafter.

Such a dramatic description must rank electrical cardioversion with Withering's description of the effect of digitalis, or Florey's account of the effect of penicillin. It probably explains why electrical cardioversion has never been subjected to a placebo-controlled trial.

Lown developed the direct current (DC) 'cardioverter' and he, and later Resnekov,<sup>5</sup> studied the use of DC cardioversion on atrial fibrillation. It was soon appreciated that patients with a short duration of atrial fibrillation corrected more readily, and needed a lower energy shock than those with atrial fibrillation which was long-standing. Lown initially claimed a high success rate - 94% conversions to sinus rhythm in 456 episodes of atrial fibrillation in 350 patients. However, in his later review (1973) Resnekov recognised that cardioversion was successful in less than 50% of cases when atrial fibrillation had persisted for ten years. He found that the cause of atrial fibrillation was not important except that successful conversion to sinus rhythm was only achieved in 70% of patients with lone atrial fibrillation, and the lack of success was correlated with a large heart on chest X-ray, or with selective enlargement of the left atrium. He was also more cautious than Lown had been six years earlier about the likelihood of sinus rhythm being maintained.

\*A background paper prepared for the Royal College of Physicians of Edinburgh Consensus Conference on Atrial Fibrillation in Hospital and General Practice.

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Lown<sup>4</sup> pointed out the safety of DC cardioversion compared with attempts at cardioversion with quinidine. Most of the patients with atrial fibrillation whom he treated by cardioversion had been given 'large and even toxic doses of quinidine', yet 96% of patients were converted without complications. As experience grew, however, it became clear that DC cardioversion is not free of risk. Some sort of general anaesthesia is needed, and ventricular arrhythmias can occur - particularly when the patient is hypokalaemic or is being treated with digoxin. Cardioversion can lead to - or perhaps, reveal - disordered sinus or atrioventricular node dysfunction, and so result in a slow rate. Cardioversion can also be associated with systemic embolization, particularly when atrial fibrillation has been present for more than a few hours.

All these problems are probably equally important with cardioversion by drugs, but in the absence of any randomised trials comparing DC and drug cardioversion it is impossible to be certain.

#### CARDIOVERSION BY DRUGS

##### *Digoxin*

Digoxin has for 200 years been the treatment of choice for rate control in patients with atrial fibrillation and heart failure, and it remains the ideal drug for this purpose because it combines lowering of the ventricular rate with an inotropic effect. There is, however, good evidence that it neither converts atrial fibrillation, nor prevents paroxysms of atrial fibrillation.

Falk *et al.*<sup>6</sup> performed a randomised, double-blind, placebo-controlled trial in 36 patients with atrial fibrillation which had persisted for a maximum of seven days. These patients had not had a recent myocardial infarction, unstable angina, thyrotoxicosis or a metabolic problem. Treatment was continued for a maximum of 18 hours. Nine of 18 patients given placebo, and eight of 18 patients given digoxin, returned to sinus rhythm. The placebo-treated patients reverted to sinus rhythm slightly more quickly than those given digoxin (mean duration of atrial fibrillation after starting treatment 3.3 hours compared with 5.1 hours).

Jordaens *et al.*<sup>7</sup> compared intravenous digoxin 125 mcg and placebo in a double blind, randomised, study of 40 patients with atrial fibrillation of less than one week's duration. One patient converted spontaneously before treatment. Conversion to sinus rhythm within 12 hours (the study endpoint) occurred in nine of 19 patients given digoxin and eight of 20 among those given placebo.

The Digitalis in Acute Atrial Fibrillation (DAAF) Trial<sup>8</sup> was a double-blind, randomised, comparison of intravenous digoxin and placebo in 239 patients with atrial fibrillation with a mean duration of 21 hours, and a maximum of seven days. At 16 hours, the defined study endpoint, 51 of 122 patients (46%) in the placebo group and 60 of 117 patients (51%) in the digoxin group had converted to sinus rhythm. The duration of atrial fibrillation was slightly, but not significantly, shorter in the digoxin group and digoxin had an immediate effect on heart rate which was not seen with placebo.

When 41 patients with paroxysmal atrial fibrillation who had not taken long-term digoxin were compared with 31 who were (not on a randomised basis) it was found that digoxin treatment was associated with significantly more prolonged attacks of atrial fibrillation, and during such attacks digoxin did not control the ventricular rate any

better than placebo.<sup>9</sup>

##### *Other single drug studies*

Uncontrolled open studies of intravenous procainamide and intravenous amiodarone in patients with atrial fibrillation have found conversion to sinus rhythm in nine of 21 and eight of 25 patients respectively. These rates are lower than those seen in the placebo groups of the digoxin studies described above; it is impossible to say whether this reflects the selection of patients who were more difficult to convert, or whether the drugs were both ineffective. The need for placebo-controlled studies is clear.

Double-blind placebo-controlled studies of flecainide, amiodarone, and sotalol have been described.

Donovan *et al.*<sup>12</sup> randomly allocated 102 patients who had had atrial fibrillation for between 30 minutes and 72 hours to treatment with intravenous flecainide or placebo. Within one hour sinus rhythm had been achieved in 29 of 52 patients (57%) given flecainide, and in seven of 52 (14%) given placebo, a highly significant difference. In a study<sup>13</sup> comparing intravenous flecainide, intravenous amiodarone, and placebo in 98 patients with atrial fibrillation, also of 30 minutes to 72 hours duration, conversion was achieved in 20 of 34 (59%) in the flecainide group, 11 of 32 (34%) in those given amiodarone, and seven of 32 (22%) in those given placebo. The differences between the groups were significant.

Finally, in a double-blind comparison of intravenous sotalol and placebo<sup>14</sup> in patients with atrial fibrillation of up to seven days duration, sinus rhythm was achieved in two of 14 (14%) patients given placebo and four of 34 (11%) of patients given different doses of sotalol - a difference that was not significant.

##### *Drug comparisons*

In addition to the placebo-controlled comparison of flecainide and amiodarone described above, a series of small studies has compared two drugs for the efficacy in converting atrial fibrillation, without any comparison with a placebo group.

Quinidine, the first drug used for conversion of atrial fibrillation has been compared with amiodarone, sotalol, and flecainide. Amiodarone and quinidine were found equally effective in a small group of patients with atrial fibrillation of more than three weeks duration: conversions achieved were quinidine eight of 17 (47%) and amiodarone 12 of 27 (44%).<sup>15</sup> Similarly, quinidine and flecainide were found similar<sup>16</sup> in a group of patients with a mean duration of atrial fibrillation of three months: conversions to sinus rhythm were 18 of 30 (65%) with quinidine and 25 of 30 (67%) with flecainide. In this study gastro-intestinal symptoms were much more common with quinidine. In comparison with sotalol, in one study quinidine led to the conversion of 24 of 28 (86%) patients while sotalol converted 17 of 33 (52%)<sup>17</sup> and this was confirmed in a second study<sup>18</sup> with 15 of 25 (60%) converting on quinidine and five of 25 (20%) on sotalol. In the first of these studies sotalol was found to be associated with bradycardia, and quinidine with broad complex tachycardia; in the second study four patients treated with quinidine developed torsade de pointes ventricular tachycardia shortly after conversion.

Flecainide has been found superior to procainamide, with 37 of 40 (92%) converting to sinus rhythm compared with 15 of 40 (37%).<sup>19</sup> It also appears more effective than

propafenone, in one study there being 18 of 20 (90%) conversions with flecainide compared with 11 of 20 (55%) with propafenone.<sup>20</sup> The consistency of the flecainide effect was also seen in comparison with verapamil, with flecainide converting 14 of 17 (82%) of patients, and verapamil converting only one of 17 (6%).<sup>21</sup> In a three-way comparison of flecainide, propafenone and verapamil the respective conversions were 32 of 37 (86%), 11 of 20 (55%) and 0 of 20.<sup>22</sup>

Verapamil has also been compared with amiodarone and with the short-acting beta blocker esmolol.<sup>23,24</sup> In the comparison with amiodarone, verapamil was virtually ineffective in converting atrial fibrillation, while in the esmolol comparison conversion rates were seven of 14 (50%) with esmolol and two of 17 (12%) with verapamil. Although there are no placebo controlled trials of verapamil, it is clearly ineffective.

There is only limited information about the effect of beta blockers. Apart from the esmolol-verapamil study, esmolol has been compared with propranolol.<sup>25</sup> The two drugs were equally effective in controlling the ventricular rate; conversion to sinus rhythm was similar but disappointing - esmolol seven of 50 (14%) and propranolol nine of 55 (16%).

None of these comparative trials included randomised groups treated by DC cardioversion, but in one there were 26 patients who had not converted with either quinidine or sotalol, and in these DC cardioversion was attempted. Sinus rhythm was restored in 19 patients. DC cardioversion is thus presumably more effective than treatment with these drugs.

#### CONCLUSIONS

- Atrial fibrillation occurs in a wide variety of clinical circumstances. There is a relatively high spontaneous rate of reversion to sinus rhythm, especially when the duration of atrial fibrillation is short. Attempts to convert atrial fibrillation are most likely to be successful when the duration of the arrhythmia is short, and the heart is not enlarged.
- Clinical trials of different methods of converting atrial fibrillation to sinus rhythm are generally small, and of poor quality.
- DC cardioversion has never been subjected to a randomised trial, but it appears the most effective method of restoring sinus rhythm. Its main disadvantage is the need for general anaesthesia.
- Digoxin is certainly of no value for converting atrial fibrillation, and verapamil is probably equally ineffective.
- Of the Class I antiarrhythmic agents, such evidence as there is suggests that flecainide is the most effective.

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## HOW DO WE ACHIEVE OPTIMAL CARDIOVASCULAR FUNCTION IN ATRIAL FIBRILLATION?\*

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### INTRODUCTION

Atrial fibrillation (AF) is a common and often disabling arrhythmia. With the onset of the event, most patients are symptomatic, some severely. Symptoms include palpitations and extend to fatigue, breathlessness, dizziness and occasionally, syncope. In general, symptoms are more severe at the onset of attacks, subsiding to a more tolerable level with attack chronicity. Some of the most disadvantaged patients are those with frequent paroxysms of atrial fibrillation rather than those in chronic stable AF.

Atrial fibrillation reduces cardiac output. There are many reasons why this occurs. They include - inappropriately rapid ventricular rate; R-R interval variability; loss of atrial transport; a ventricular myopathy and disturbed chronotropic responses to exercise. Obviously, optimal cardiovascular function of a patient subject to atrial fibrillation is achieved by restoring and maintaining sinus rhythm.<sup>1</sup> When this is not possible, the ventricular response rate of chronic or permanent atrial fibrillation can be controlled to provide the best cardiac function for any given physiological circumstance. Such does not necessarily address cycle length variability and will not restore the atrial contribution to cardiac output.

### DELETERIOUS EFFECTS OF AF ON CARDIAC OUTPUT

Many attempts have been made to determine which of the variety of factors present in atrial fibrillation contributes most to the reduction of cardiac output.<sup>2</sup> Studies have been conducted in animals, in human volunteers and in patients with atrial fibrillation. The issue is complicated as the diseased heart responds differently to atrial fibrillation than does the normal heart.

#### *Effect of loss of atrial contribution*

The effect of the atrial contribution to cardiac output has been investigated in dual chamber paced patients with AV block by varying the AV timing. Atrial augmentation to cardiac output has been shown to be dependent upon the AV coupling interval which, in turn, is a rate-dependent variable. These experiments do not exactly reproduce the situation with atrial fibrillation but when the atrial contraction is timed to occur during ventricular systole, it is reasonable to conclude that there is no atrial contribution to cardiac output. In heart failure patients, it has been judged that the atrial contribution to cardiac output may be as much as 20%.<sup>3</sup> In normal individuals, this reduction in cardiac performance would not be noticed at rest, nor

indeed, on even moderate exercise. It would require severe maximal exercise to bring out the abnormality. In diseased individuals this reduction would be expected to have considerable practical impact.<sup>4</sup>

#### *Effect of variable R-R intervals*

Cardiac rhythm is rarely ever absolutely regular but in atrial fibrillation there are remarkable variations in R-R interval whether or not antiarrhythmic drugs are being prescribed. In sinus rhythm in the normal heart, the AV timing is modulated by the preceding cycle length. This maximises the atrial contribution. In atrial fibrillation where there is no atrial contribution, ventricular filling depends on the diastolic interval. When the diastolic interval is abbreviated to 300 ms or less, it is likely that filling is markedly incomplete and cardiac output will suffer.

Beat-to-beat contractile studies have shown that the Frank Starling mechanism can optimise cardiac contracting of the human heart in response to RR interval variability.<sup>5,6</sup>

There is growing evidence that the left ventricle is abnormal during AF. In some patients, the cause may relate to underlying cardiac disease being responsible for both LV dysfunction and AF, e.g. ischaemic heart disease, rheumatic heart disease, hypertension, etc. In even normal individuals, however, (lone AF) the LV may not contract properly raising the possibility of a tachycardia - cardiomyopathy. The best evidence for this comes from studies of patients post cardioversion in whom return of LV contractile function may take weeks or months.<sup>7</sup>

#### *Chronotropic incompetence*

In a normal heart, ventricular rate is controlled through the sinus node to produce a cardiac output appropriate for metabolic demand. In the fibrillating heart, the AV node processes impulses dependent upon its refractory period and to some extent, dependent upon concealed penetration of the AV node from its multiple inputs. The result is a ventricular response rate which may bear little relationship to metabolic need. The ventricular rate, however, is not just free-running. Autonomic effects on the AV node alter its conduction and refractoriness offering some modulation.<sup>8,9</sup> Unfortunately, in both the treated and untreated patient, sympathetically driven AV nodal effects can produce very rapid and potentially detrimental ventricular rates.<sup>10</sup>

### CONTROLLING THE VENTRICULAR RESPONSE RATE IN ATRIAL FIBRILLATION

The major detriment to cardiovascular function in atrial fibrillation is the inappropriately rapid ventricular response rate. Ultimate control of ventricular rate would be provided by restoring sinus rhythm. In permanent atrial fibrillation this is not possible.

#### *Digoxin monotherapy*

Traditionally, digoxin has been used to slow the ventricular

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response rate. In this regard it is an effective therapy but its capability to slow exercise-related excursions of rate response in atrial fibrillation is poor. Assessing the adequacy of rate control is made more difficult by a lack of agreed rate limits. 'Adequate' rate control is often judged by patients' symptomatology but there is a growing trend to review Holter captured diurnal variability, particularly when atrial fibrillation affects individuals whose job demands a minimal risk of cardiovascular incapacitation, e.g. pilots, oil rig workers, etc.

#### *Digoxin + beta blocker*

Co-prescription of a beta blocker with digoxin would seem an appropriate approach to improving rate control. Several small studies have examined this combination concluding that, indeed, exercise-induced excursions of ventricular response rate can be blunted by the combination therapy more effectively than by digoxin monotherapy alone. Brodsky *et al.*<sup>11</sup> compared the rate control offered by digoxin alone and digoxin + dl sotalol. The study was randomised, double blind and controlled. The combination was superior to monotherapy in respect of rate control but symptoms were similar. No adequate study has shown statistically significant evidence of improved effort capacity. At individual patient level, there are those whose rate control is uninfluenced by the co-prescription of the beta blocker. Channer *et al.*<sup>12</sup> presented the case for adding a beta blocker with partial agonist activity to digoxin therapy rather than using atenolol. In eight patients, atenolol and pindolol were added to digoxin in a single blind crossover design. Symptoms and heart rate control were better with either beta blocker but on atenolol, there were nocturnal pauses.

#### *Co-prescription of digoxin plus calcium antagonist*

The AV nodally active calcium antagonists, verapamil and diltiazem, have been used in combination with digoxin to improve rate control. Lang *et al.*<sup>13</sup> reported a statistically significant improvement in exercise capacity when verapamil was given with digoxin. In other studies, blunting of exercise heart rates has been shown but there has been little or no evidence of exercise improvement. Verapamil has significant first pass hepatic metabolism and a relatively short half-life. Slow release versions may be better than conventional verapamil for this indication. Diltiazem does not undergo such metabolic effects and is an alternative.

#### AV NODE ABLATION

The ultimate solution to rate control may lie with AV node ablation and subsequent ventricular pacing. This procedure held modest attraction when the ablative energy source was a DC shock. With the advent of controllable and much less traumatic RF energy delivery, ablation is finding great favour and some have even advocated its near first-line use. The technique is relatively safe and has a success rate of 95% or better. The disadvantage is that the atria still fibrillate posing a continuing thromboembolic risk and offering no contribution to cardiac output. The ventricles must be paced. The potential disadvantage of the abnormal ventricular activation of pacing may be offset by the advantage of a regularised rate and a rate that can be sensor-modified (VVIR pacing) to accord with bodily demands.

In relatively small studies, considerable symptomatic benefit has been reported for patients undergoing the procedure. These patients have usually been those in whom

medical therapy has failed or who are intolerant of therapy. The studies have reported increased performance effects as well as improvements in quality of life. Brignole *et al.*<sup>14</sup> showed significant symptomatic and functional benefit of RF ablation of the AV node in 23 patients at 15 days after the procedure. Exercise duration was increased by 15% by three months. Brignole *et al.*<sup>15</sup> compared RF AV node ablation and DDDR pacing with drug therapy in 43 patients with paroxysmal atrial fibrillation. Ablation and pacing was superior with a 46% increase in effort tolerance. Buben *et al.*<sup>16</sup> reviewed 159 patients who had undergone RF ablation of the AV node. Quality of life, as assessed by SF-36 scores was significantly improved by the procedure. Buys *et al.*<sup>17</sup> reported 25 consecutive patients who had undergone AV node ablation and VVIR pacing. All had been refractory to drugs. Exercise capacity significantly increased (although VO<sub>2</sub> was unchanged). Kim *et al.*<sup>18</sup> reported 64 patients following AV node ablation and pacing for drug refractory AF and atrial flutter. Symptoms were impressively improved (83%) with parallel reductions in NYHA status. Lau *et al.*<sup>19</sup> 'randomised' 55 patients to AV node ablation and pacing or to continued medical therapy (46 ablation, nine drugs). Over two years of follow-up there were marked symptomatic benefits in favour of those ablated with a concomitant but more modest improvement in exercise time (13 to 15 minutes). Medically treated patients showed no change.

AV node ablation is considered very safe but late sudden deaths have been reported.<sup>20</sup> The mechanism is uncertain but there are suggestions that the problem is reduced (not eliminated) by faster basic pacing rates. Currently, there are large-scale clinical trials evaluating this strategy against medical methods of rate control.

#### *AV nodal modification*

A variation of AV node ablation has been proposed whereby radiofrequency energy alters but does not destroy conduction through the AV node. The RF energy delivery is in the region of the AV node and it is thought that the effects are mediated by damage to the AV nodal inputs.<sup>21</sup> Successful modification produces a situation in which ventricular response rates are controlled without the need for pacing. The fibrillating atria remain a thromboembolic risk and do not contribute to cardiac output. The ventricular rate is modulated by autonomic effects on the AV node and can provide a 'physiological' response to exercise. The ventricular response rate is irregular as the electrical driving force for the ventricles remains the fibrillatory atrial waves which bombard the now modified AV node.

RF modification of the AV node is successful in about 75% of patients.<sup>22</sup> In the remaining 25% complete heart block is created and they therefore require permanent pacing. Although not the intention of the original procedure, this outcome is not a disaster. On the contrary, these patients will benefit as discussed previously for AV nodal ablation. Follow-up at three months has shown that the initial benefits of the procedure in respect of maximal daytime heart rate and exercise provoked heart rate are maintained. Recent longer-term follow-up<sup>23</sup> confirms continuing benefit with significant symptomatic and exercise capacity improvements. Nonetheless, larger studies are required as are more long-term follow-up data.

CONCLUSIONS

Sinus rhythm is an inherently more efficient cardiac rhythm than atrial fibrillation. If the patient cannot be returned to sinus rhythm from atrial fibrillation, then therapy is directed to controlling the ventricular rate. Remarkably, there are no established and agreed criteria for what constitutes adequate or even good rate control. It may well be that there are large intra-individual variations in such figures depending upon disease state, etc.

RF procedures for rate control are being scientifically investigated and already there are good data. By contrast, drug control has been poorly tackled with few well-designed clinical trials and with only small patient populations.

Medical control of ventricular rate has not been aggressively pursued. There is increasing realisation that digoxin monotherapy may not control exercise-related excursions of heart rate and there is growing evidence that co-prescription of a beta blocker or an electrically active calcium entry blocker with digoxin may be preferable.

Dissatisfaction with medical therapy for controlling ventricular rate has led to the techniques of AV node ablation and AV node modification. To date, most of the patients undergoing such procedures have failed conventional medical regimens. In these patients, there is evidence that the improved rate control is associated with marked reduction in symptomatology and improvements in effort capacity. These would strongly suggest amelioration of cardiovascular function and in small studies such has been confirmed. By contrast, and somewhat puzzlingly, better rate control offered by medical therapy has been much more difficult to evaluate with little clear evidence that cardiovascular function is improved. Were it not for cost and for the small but not unimportant risks of RF ablation and pacing, a case could easily be made for this being first-line management. Extrapolation of benefit seen in medically failed patients to a more general AF population

is not justified at present. Until the ongoing large-scale randomised studies report, medical control should remain first-line management.

PRACTICE POINTS

- Regardless of management, AF has a haemodynamic cost compared to sinus rhythm. *Grade A*
- The haemodynamic detriment of AF is principally related to inappropriate rate response with more modest contributions from the lack of atrial systole, cycle length irregularity, etc. *Grade A*
- ‘Good’ or ‘adequate’ rate control is undefined. Most would agree that resting rates should not exceed 100 bpm nor exercising rates 200 bpm. These are crude and probably inappropriate criteria. *Grade C*
- Digoxin monotherapy controls resting heart rate in AF but offers poor control of exercise rate. *Grade B*
- Digoxin with either a beta blocker or an electrically active calcium entry blocker (verapamil, diltiazem) offers better rate control than digoxin alone but evidence of improved cardiac function or increased effort capacity is scant. *Grade B*
- RF ablation of the AV node with rate responsive pacing offers the best control of rate. Good evidence exists for both symptomatic and objective functional benefit. Cost, availability and a concern about late sudden death have tempered enthusiasm. Large-scale clinical trials are underway comparing this approach with medical control of rate. They will report in the next 18 months. Until then, RF ablation should be reserved for those who fail or do not tolerate drug therapy. *Grade B*
- RF modification of the AV node can control rate without pacing. Recent long-term data are encouraging but more studies are needed. *Grade C*
- Table 1 illustrates the advantages and disadvantages of current medical and RF techniques.

TABLE 1  
Impact of rate control therapies for permanent atrial fibrillation.

	<b>Thrombo-embolic risk</b>	<b>Atrial transport</b>	<b>Ventricular activation</b>	<b>Resting heart rate</b>	<b>Exercise heart rate</b>	<b>Rate response</b>	<b>Symptom benefit</b>	<b>Haemo-dynamic benefit</b>
Digoxin monotherapy	Continues	None	Normal	Controlled	Not controlled	Inappropriate	√	√
Digoxin+ betablocker	Continues	None	Normal	Controlled	Controlled	Appropriate	√√	√
Digoxin+ CEB	Continues	None	Normal	Controlled	Controlled	Appropriate	√√	√
RF ablation+ VVI	Continues	None	Abnormal	Controlled	Controlled	None	√√	√√
RF ablation+ VVIR	Continues	None	Abnormal	Controlled	Controlled	Appropriate	√√√	√√√
RF modification	Continues	None	Normal	Controlled	Controlled	Appropriate	√√√	√√√

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## PRIMARY PREVENTION OF STROKE IN PATIENTS WITH ATRIAL FIBRILLATION\*

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### BACKGROUND

About one in six ischaemic strokes is associated with nonvalvular atrial fibrillation (AF).<sup>1,2</sup> This frequency increases with patient age, so more than one-third of ischaemic strokes in people over age 75 occur in people with AF.<sup>2-4</sup> AF is a potent independent risk factor for ischaemic stroke.<sup>5,6</sup> Randomised trials have demonstrated that antithrombotic therapies are efficacious for stroke prevention in AF,<sup>7-10</sup> and hence detection of AF offers an important potential opportunity for stroke prevention.

### METHODS

The English language literature between 1982-1998 was searched with the PLUSNET computerised retrieval system, combining key words of atrial fibrillation with stroke, embolism or thromboembolism. The reference lists of articles that emerged were also searched for additional sources. This review focuses on ten randomised clinical trials,<sup>8,11-21</sup> meta-analyses,<sup>7,10,22-24</sup> and selected longitudinal cohort studies analysing risk stratification.<sup>7,25-32</sup> When possible, the number of patients that would need to be treated yearly ('number-needed-to-treat') to prevent one stroke was calculated as an index of the therapeutic impact, as well as number of events prevented per 1,000 patients treated.<sup>33</sup>

### RISK FACTORS FOR STROKE IN AF

The annual rate of ischaemic stroke among people with AF without prior stroke or TIA is about 5%/year, with wide, clinically important variations (0.5-11%/yr) among well-defined subpopulations of AF patients.<sup>7,9,30-32</sup> Multivariate analyses of prospective studies with large numbers of ischaemic strokes consistently show hypertension, prior TIA/stroke and left ventricular systolic dysfunction to be independently predictive of stroke in AF patients.<sup>7,22,27-30,34</sup> Other studies have variably linked stroke in AF patients to coronary artery disease, diabetes, age and perhaps female gender.<sup>7,27,29,30</sup> About one-third of AF-associated stroke occurs in patients with intermittent (paroxysmal) AF. Patients with intermittent AF tend to be younger with less associated cardiovascular disease than those with sustained AF, and their risk of stroke is, on average, lower. However, intermittency of rhythm does not appear to independently influence stroke risk when other risk factors are considered.<sup>29</sup>

The relationship of stroke in AF patients to increased left atrial diameter has been inconsistent.<sup>22,28,29</sup> The presence

of substantial mitral regurgitation (5-10% of AF patients) confounds the relationship between left atrial diameter and embolic risk, as it is associated with an enlarged left atrium but with a decreased risk for atrial thrombi and stroke.<sup>35</sup> Transoesophageal echo cardiographic studies support an association of both spontaneous echodensities and left atrial thrombi with subsequent stroke in patients with AF, but the predictive value is limited by lack of specificity (perhaps related to differing acquisition techniques and criteria).<sup>32,36</sup>

Risk stratification schemes have been derived from analysis of AF patients participating in clinical trials (Table 1). The stratification scheme from the pooled analysis of control patients from five clinical trials considered criteria that differed slightly between the studies, contributing to a conservative (i.e., only about 10% of participants were categorised as low-risk) but robust scheme.<sup>7,25</sup> Left ventricular dysfunction detected by echocardiography or by a clinical history of heart failure was a predictor of stroke in a subsequent pooled analysis of three of these trials (those which collected detailed echocardiographic data).<sup>22</sup> The SPAF III Study model<sup>29</sup> applies to AF patients taking aspirin and has been validated as predictive in a subsequent prospective study by the same investigators.<sup>30</sup> Of note, the reliability of these risk stratification schemes when applied in clinical practice or to population-derived cohorts of AF patients remains to be fully defined.<sup>26</sup>

### ORAL VITAMIN K ANTAGONISTS FOR STROKE PREVENTION: EFFICACY, SAFETY AND OPTIMAL INTENSITY

The efficacy of anticoagulation with oral vitamin K antagonists for prevention of ischaemic stroke in nonvalvular AF has been established by recent randomised clinical trials.<sup>8,9,11-19</sup> Aggregate analysis of five clinical trials of primary prevention shows that anticoagulation with warfarin reduces ischaemic stroke by 68% ( $p < 0.001$ ) compared to the rate in untreated patients (Table 2); on-therapy analysis indicates an even greater benefit.<sup>7</sup> The rate of stroke, systemic embolism or death was reduced 48% ( $p < 0.001$ ) by warfarin.<sup>7</sup> The absolute increase in the rate of severe haemorrhage among elderly, anticoagulated AF patients in these clinical trials was 0.3% - 2%/year with target International Normalized Ratio (INR) ranges of 1.4-4.5.<sup>7,16</sup> However, patients included in these trials were carefully selected to minimise bleeding risks and were followed closely on protocols. Whether such low bleeding risks can be routinely achieved in clinical practice is a crucial issue.<sup>37</sup>

The risk of major haemorrhage among elderly AF patients taking warfarin is related to the intensity of anticoagulation, patient age and fluctuation in INRs.<sup>38-41</sup> Randomised trials with target INRs between 2.7 and 4.8 show a tenfold increase in intracranial bleeding among elderly patients given anticoagulants vs. placebo.<sup>42-45</sup> A case-control study involving a relatively young cohort (about half < 65 years old), found that the rate of anticoagulation-associated

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TABLE 1  
Risk stratification schemes for patients with nonvalvular atrial fibrillation\*

	High-risk	Moderate-risk	Low-risk
<b>AFI/ACCP Consensus</b> <sup>7,25</sup>			
Criteria	History of Hypertension Diabetes Prior stroke or TIA Coronary artery disease Congestive heart failure	Age $\geq$ 65, <sup>#</sup> no high-risk features	Age < 65, no high-risk features
% of study cohort	75%	15%	10%
Stroke risk, no therapy	$\approx$ 6%/yr	$\approx$ 2%/yr <sup>#</sup>	$\approx$ 1%/yr
<b>SPAF III Study</b> <sup>29,30</sup>			
Criteria	Systolic BP >160mmHg Left ventricular dysfunction <sup>##</sup> Prior stroke or TIA Women > 75 years old	History of hypertension, no high-risk features	No high risk features or history of hypertension
% of study cohort	50%	25%	25%
Stroke risk with aspirin (95%CI)	$\approx$ 8%/yr ** (5.9-10.6)	$\approx$ 3.5%/yr <sup>@</sup> (2.5-5.2)	$\approx$ 1%/yr (0.6-2.0)

\* In the AFI Pooled Analysis,<sup>7</sup> most patients received placebo while about half of participants in one trial used aspirin. The stratification scheme from the SPAF III Study<sup>29,30</sup> applies during treatment with aspirin 325 mg/day. Events were ischemic strokes plus a small number of systemic emboli in the SPAF studies.

SPAF = Stroke Prevention in Atrial Fibrillation Study; AFI = Atrial Fibrillation Investigators; ACCP = American College of Chest Physicians; CI = confidence intervals; H = history; TIA = transient ischemic attack; AF = atrial fibrillation.

@ The rate of disabling ischemic stroke (Rankin II or more assessed 1-3 months later) was 1.4%/yr.<sup>30</sup>

## Impaired left ventricular function included recent congestive heart failure or fractional shortening  $\leq$  25% by M-mode echocardiography.

\*\* For those without prior stroke/TIA, the estimated event rate was  $\approx$ 6%/yr, while for those with prior stroke/TIA it was nearly 12%/yr.

# In the AFI/ACCP Consensus conference scheme, the ischemic stroke rate in those without high-risk features was 1.6%/year in the age group 60-69, 2.1% in those 70-79, and 3.0%/year in those over age 80.<sup>7</sup>

brain haemorrhage was not importantly increased until INRs exceeded 4.<sup>39</sup> Intracranial haemorrhage complicating anticoagulation is usually fatal, and its frequency is age-related.<sup>38,39,45</sup>

The optimal target intensity of anticoagulation to prevent stroke and minimise bleeding risk in AF is controversial and may vary between subgroups of AF patients. A target INR range of 2-3 for primary prevention of stroke in AF patients was derived by consensus from consideration of five clinical trials which tested target INRs ranging between 1.4-4.5 (Table 2) and is supported by a case-control study.<sup>34</sup> No direct randomised comparisons of target INRs within this range have been done. The two clinical trials with target INRs between 1.4 and 2.8 (estimated) reported the greatest efficacy (Table 2).<sup>12,14</sup> Secondary analyses of the SPAF III trial<sup>8</sup> and a case-control study<sup>34</sup> suggest that INRs  $\geq$  1.6 offer substantial protection against ischaemic stroke, which becomes maximal with an INR of about 2.0 (Figure 1).<sup>46</sup> A secondary analysis of a large randomised trial of AF patients with recent TIA or minor stroke suggested more intensive anticoagulation target (INR range of 2.0-3.9) to be optimal when ischaemic stroke plus other major vascular events are considered.<sup>47</sup>

The optimal target INR for AF patients over age 75 years balancing protection against stroke versus bleeding is unresolved in our view. Support for a target range of 2.0-3.0 is found in the low rate (0.3%/yr) of intracranial bleeding among AF patients over age 75 in combined analysis of four clinical trials,<sup>23</sup> and a case-control study suggesting that intracranial haemorrhage during anticoagulation is not importantly increased until the INR exceeds 4.<sup>39</sup> However, the achieved INRs in patients over age 75 in the four clinical trials is unknown and, based on the achieved INRs in these studies, likely averaged well below 2.5.<sup>12-15</sup> Patients analysed in the case-control study<sup>39</sup> were much younger on average, and the threshold INR level associated with important increases in intracranial haemorrhage for those > 75 years old is not known. In the only clinical trial specifically focusing on AF patients over age 75 years, a mean achieved INR of 2.6 during follow-up was associated with a substantial (1.8%/yr) rate of intracranial haemorrhage that offset the reduction in ischaemic stroke.<sup>16</sup> While the confidence intervals around this rate were wide, this result raises concern for some about the safety of achieved INRs > 2.5 for AF patients over age 75.

Because major haemorrhage during anticoagulation is

TABLE 2  
Antithrombotic therapies in atrial fibrillation: randomised trials of primary prevention.

Study	N	Target INR or aspirin dose	Ischaemic stroke		
			Relative risk reduction <sup>##</sup>	P	Absolute rate reduction
<b>Warfarin<sup>a</sup>-vs. placebo<sup>b</sup></b>					
• AFASAK <sup>13</sup>	671	2.8 - 4.2	58%	< 0.05	
• SPAF I <sup>11</sup>	421	2.0 - 4.5 <sup>###</sup>	65%	0.01	
• BAATAF <sup>14</sup>	420	1.5 - 2.7 <sup>###</sup>	86%	0.002	
• CAFA <sup>15</sup>	378	2.0 - 3.0	33%	NS	
• SPINAF <sup>12</sup>	525	1.4 - 2.8 <sup>###</sup>	79%	0.001	
<b>Aggregate<sup>7</sup></b>	<b>2313</b>		<b>68%</b>	<b>&lt;0.001</b>	<b>±3%/yr</b>
<b>Aspirin<sup>a</sup>-vs. placebo<sup>b</sup></b>					
• AFASAK <sup>13</sup>	672	75 mg/day	18%	NS	
• SPAF I <sup>49</sup>	940	325 mg/day	36%	NS	
<b>Aggregate<sup>10</sup></b>	<b>1612</b>		<b>25%</b>	<b>NS</b>	<b>±1%/yr</b>
<b>Warfarin<sup>a</sup>-vs. aspirin<sup>b</sup></b>					
• SPAF II <sup>16</sup>	1100	See above	31%	NS	
• AFASAK <sup>13</sup>	671	See above	50%	0.05	
• PATAF <sup>17</sup>	729	-	Pending	—	—
• AFASAKII <sup>19</sup>	339	2.0-3.0	-13%	NS	
<b>Aggregate</b>	<b>2839</b>		<b>45 %</b>	<b>NS</b>	<b>± 2%/yr</b>
<b>Warfarin<sup>a</sup> vs low-dose warfarin plus aspirin<sup>b</sup></b>					
• SPAF III <sup>8</sup>	650	**	79%	.001	
• AFASAKII <sup>19</sup>	341	**	18%	NS	

\* Patients with nonvalvular atrial fibrillation in relatively large, published randomised trials; an additional small randomised trial tested low molecular weight heparin.<sup>18</sup> Several include 3-8% of patients with remote thromboembolism; these are excluded when possible using published data.

<sup>##</sup> Reduction by treatment 'a' vs. 'b', intention-to-treat analysis.

<sup>###</sup> INR estimated for BAATAF, SPAF I, and SPINAF, which used prothrombin time ratios.

\*\* SPAF III participants were those with a high (> 6%/yr) rate of stroke if given aspirin alone, treatment arms were target INR 2.0-3.0<sup>a</sup> vs. INR 1.2-1.3<sup>b</sup> plus aspirin 325 mg/day; in AFASAKII, treatment arms were target INR 2.0-3.0<sup>a</sup> vs. warfarin 1.25 mg/day plus aspirin 300 mg/day.

age-related, using the lowest adequate intensity of anticoagulation is particularly important for elderly AF patients. Analyses combining AF patients of all ages support that maximal protection against ischaemic stroke is probably achieved with INRs between 2.0 and 3.0.<sup>8,34,46</sup> However, INRs between 1.6 and 2.5 provide substantial, if partial, efficacy (estimated to be nearly 90% of the higher intensities, Figure 1).<sup>8,34</sup> Given the uncertainty about the safety of INRs > 2.5 for AF patients over age 75, a target INR of 2.0 (range 1.6-2.5) may be a reasonable compromise between toxicity and efficacy for this age group, pending further data about the safety of higher intensities. The efficacy of target INRs of 1.4-2.8 (estimated) for AF patients over age 70 has been demonstrated.<sup>12</sup> In recent clinical trials involving elderly participants, *achieved* INRs during follow-up were more often below the target range than above it. When low-intensity target ranges are chosen, special efforts to minimise the time spent below the target range (during which stroke protection is sharply reduced) is critically important. Alternatively, a target INR range of 2.0-3.0 seeking

maximal protection against ischaemic stroke is recommended for AF patients of all ages by those who believe this range to be relatively safe.<sup>48</sup>

#### ANTIPLATELET AGENTS FOR STROKE PREVENTION IN AF PATIENTS

The efficacy of aspirin, a platelet anti-aggregation agent, for primary prevention of stroke in AF patients has been assessed in two double-blinded, placebo-controlled clinical trials of primary prevention,<sup>11,13,49</sup> yielding a pooled risk reduction of 25% (p = NS) compared to placebo (Table 2).<sup>10</sup> Aspirin was significantly less efficacious than warfarin.<sup>13,16</sup> Of note, pooled analysis of these two trials with two trials of secondary prevention shows a reduction in stroke of 21% (p = 0.03) and stroke, myocardial infarction or vascular death of 19% (p=0.04).<sup>7,20,21</sup> Clinical trials of primary prevention suggest that warfarin reduces the risk of ischaemic stroke by about 45% compared to aspirin in AF patients (Table 2). Even low-dose aspirin increases the risk of major haemorrhage nearly twofold (by about 0.5%

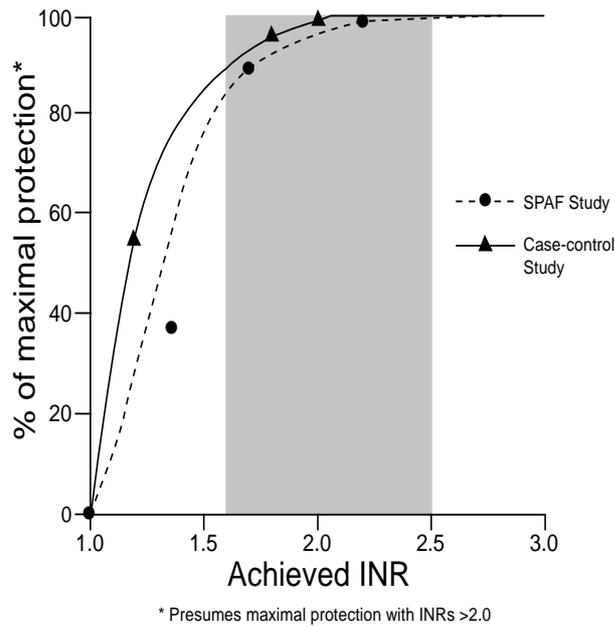


FIGURE 1

Relative efficacy of target INRs of 1.6 - 2.5. Achieving INRs equally distributed in the range of 1.6 - 2.5 is predicted to provide 95% of the protection of INRs between 2.0 - 3.0 for primary prevention of stroke in patients with nonvalvular atrial fibrillation. For those with a stroke rate of 6%/yr, the difference in stroke rates between INRs achieved in these two target ranges would be about 0.2%/yr (number needed to treat with the higher intensity for one year to prevent one additional stroke would be about 450). Data from table 4 from Hylek et al.<sup>34</sup> and the Stroke Prevention in Atrial Fibrillation Investigators<sup>8</sup> (reprinted with permission of the American College of Physicians).<sup>46</sup>

/yr in elderly people).<sup>50</sup>

Other antiplatelet agents have been tested for secondary prevention of stroke in AF patients and may prove superior to aspirin, although further studies are required to better define their role.<sup>20,21,51</sup>

REDUCTION IN VASCULAR EVENTS ACCORDING TO INHERENT RISK

Because of the widely varying rates of stroke in untreated AF patients, the benefit of antithrombotic therapies for preventing stroke differs importantly between patient subgroups (Table 3, Figure 2). Among AF patients with ischaemic stroke rates of 1%/yr during treatment with aspirin, only small reductions in ischaemic stroke would accrue from anticoagulation and would likely be offset by intracranial bleeding. On the other hand, high-risk AF patients have much larger reductions in stroke when anticoagulated.<sup>8</sup> Hence, risk stratification identifies AF patients who would benefit most and least from anticoagulation. The reliability of current risk stratification schemes (Table 1) when applied in general clinical practice warrants further study.<sup>26</sup> The threshold for perceived benefit from anticoagulation should also consider individual bleeding risk during anticoagulation and patient preferences.<sup>52-54</sup>

DOES RESTORATION OF SINUS RHYTHM REDUCE STROKE?

Based on the pathophysiological concept that most AF-

associated strokes are due to embolism of stasis-induced thrombi from the left atrial appendage, restoration and maintenance of atrial contractility should logically reduce thromboembolic risk. Further, left ventricular function can improve after cardioversion, potentially lowering embolic risk and improving cerebral haemodynamics. However, there is no solid clinical evidence that cardioversion followed by prolonged maintenance of sinus rhythm effectively reduces thromboembolism in AF patients. It is unclear at present whether efforts to restore and maintain sinus rhythm for the specific purpose of preventing stroke are effective and of overall benefit.

CONCLUSIONS AND RECOMMENDATIONS:

Many patients with nonvalvular AF have substantial rates of stroke, and efforts at primary prevention are warranted. Anticoagulation with oral vitamin K antagonists has been shown to be remarkably efficacious and relatively safe for primary prevention of stroke for patients with nonvalvular AF. Further studies both of the safety of anticoagulation (particularly in the very elderly, under-represented in clinical trials) and the reliability of risk stratification in clinical practice would enhance optimal use of this therapy. Aspirin offers modest benefit to those who cannot receive anticoagulants and perhaps to those at low risk of stroke when anticoagulation is not believed to be indicated.

- The inherent risk of stroke should be considered in selection of AF patients for lifelong anticoagulation (Table 4). There is no general consensus on specific criteria for stratifying stroke risk in AF patients. Pending further studies, either of the risk stratification schemes outlined in Table 1 seems reasonable.

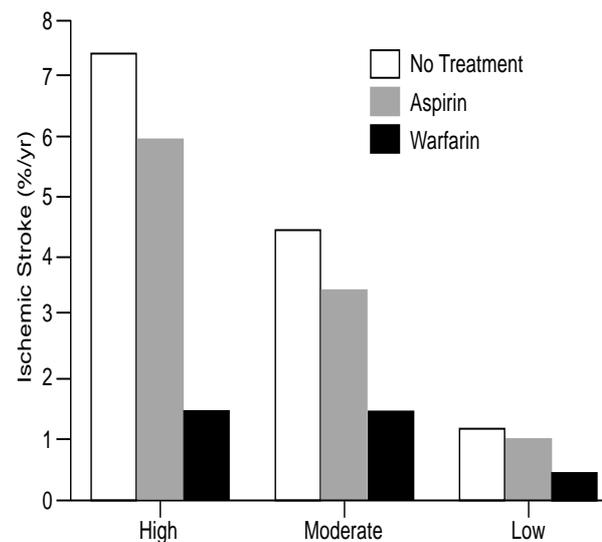


FIGURE 2

Absolute reduction in ischemic stroke by aspirin and warfarin according to the intrinsic stroke rate. Rates shown are general estimates, but illustrate the large differences in benefit conferred by risk stratification.

TABLE 3  
Anticoagulation in nonvalvular atrial fibrillation: effect of risk stratification.

Risk Group #	Stroke rates Untreated	Stroke rates on aspirin	NNT with warfarin instead of ASA for one year to prevent one ischemic stroke*	Number of strokes saved/1,000 given warfarin instead of ASA*
Unselected AF	5%/yr	4%/yr	50	20
Low-risk AF	1.2%/yr	1%/yr	200	5
Moderate-risk AF	4.5%/yr	3.5%/yr	57	18
High-risk - no prior stroke/TIA	8%/yr	6%/yr**	22	45
High-risk - prior stroke/TIA	12%/yr	10%/yr	13	75

Calculations are based on a 50% risk reduction by adjusted-dose warfarin relative to relative to aspirin in unselected, low-risk and moderate-risk patients and on a 75% risk reduction among high-risk patients, and assuming that half of strokes are disabling. Calculations do not include hemorrhagic stroke (most disabling), with three conservatively estimated to occur each year for every 1000 patients given warfarin instead of aspirin. See Green *et al.*<sup>24</sup> for alternative calculations. NNT= number needed to treat; ASA= aspirin; AF= nonvalvular atrial fibrillation. Patients with multiple risk factors (Table 1) have higher stroke rates, and consequently the number needed to treat is smaller. See Table 1 for criteria.

TABLE 4  
Prevention of stroke in nonvalvular atrial fibrillation - recommendations.

Risk group	Recommended therapy	Alternatives
Primary Prevention		
'Lone' AF under age 60	None	Aspirin
Low-risk*	Aspirin ##	Warfarin INR 1.6-3.0
Moderate-risk*	Aspirin or warfarin#	-
High-risk*		
- ≤ 75 years old	Warfarin INR 2.5 (range 2.0-3.0)	Aspirin if warfarin contraindicated
- > 75 years old	Warfarin INR 2.5 (range 2.0 - 3.0) or Warfarin INR 2.0** (range 1.6 - 2.5)	Aspirin if warfarin contraindicated
Prior stroke or TIA	Warfarin INR 3.0 (range 2.5 - 4.0)	Warfarin INR 2.5 (range 2.0 - 3.0), aspirin if warfarin contraindicated

\* See Table 1 for risk stratification schemes. Some recommend warfarin for all AF patients who can safely receive it based on lack of confidence that low- risk and moderate-risk AF patients can be reliably identified. Low- and moderate risk AF patients who are not anticoagulated must be followed carefully for development of high-risk features, which would favor the use of warfarin.

\*\* A target INR of 2.0 is a reasonable option because of concerns for bleeding in patients over age 75 years (see text), however many authorities recommend a target INR of 2-3 for AF patients regardless of age.

# Consideration of patient preferences and individual bleeding risks during anticoagulation is seen as particularly important in this group, for whom the absolute rate reduction in stroke by warfarin may be modest (See Table 3).

## There is no firm evidence favoring any specific aspirin dose; 325mg/ day enteric -coated was efficacious and well-tolerated in one double-blind trial.<sup>11</sup>

- Patients with AF should be considered for treatment with adjusted-dose warfarin to prevent stroke. For high risk or moderate-risk AF patients aged 75 years or younger deemed safe candidates for anticoagulation, a target INR of 2.5 (range 2.0-3.0) is recommended. For those over age 75 years, a slightly lower target INR 2.0 (range 1.6-2.5) may be sensible to minimise bleeding, particularly for elderly patients at special risk of bleeding. Because the relative efficacy of this lower intensity of warfarin has not been separately established for high risk AF patients in this age group, a target INR of 2.5 (range 2.0-3.0) is a reasonable alternative for AF patients of all ages.
- Aspirin (325 mg/day) maybe be indicated for AF patients who are deemed unable to receive anticoagulants or who are predicted to have low or moderate risks of stroke (Table 1). Aspirin has not been established to be efficacious for these specific subgroups of AF patients by clinical trials.<sup>10,49</sup> AF patients deemed at low or moderate risk for stroke and who are not given warfarin should be periodically evaluated for development of high-risk features favouring anticoagulation.
- Whether AF patients categorised as moderate risk by current risk stratification schemes benefit importantly from anticoagulation is controversial. The choice of antithrombotic prophylaxis for these patients should particularly consider patient preferences and individual bleeding risk during anticoagulation. Physicians who doubt the reliability of clinical criteria for distinguishing those moderate from high-risk favour the use of warfarin.

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# HOW DO WE PREVENT THROMBOEMBOLISM IN ATRIAL FIBRILLATION? - SECONDARY PREVENTION\*

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## INTRODUCTION

Atrial fibrillation (AF) is a common dysrhythmia, affecting 2-5% of the general population over the age of 60.<sup>1-3</sup> It can be found in about 15% of all stroke patients,<sup>4,5</sup> and in about 2-8% of transient ischaemic attack (TIA) patients.<sup>6-8</sup> The incidence of ischaemic stroke in AF patients without rheumatic heart disease (RHD), so-called non-rheumatic atrial fibrillation (NRAF), is about 4.5% per year. Following an initial embolism, the stroke recurrence rate is 12% per year, and the annual mortality rate is 5%.<sup>9</sup>

Since the early nineties, several large clinical trials have investigated the value of anticoagulation in the prevention of stroke and other vascular complications in patients with NRAF.<sup>10-15</sup> In addition, trials have studied the value of antiplatelet drugs.<sup>10,11,15,16</sup> Several studies have focused on stroke prevention in NRAF patients without a recent TIA or minor stroke (primary prevention),<sup>10-14</sup> whereas others have specifically addressed the prevention of recurrent vascular events in NRAF patients with recent cerebral embolism (secondary prevention),<sup>15-17</sup> and yet another trial addressed stroke prevention in high-risk NRAF patients.<sup>18</sup>

In this article we present an overview of the trials aiming at stroke prevention in high-risk NRAF patients and those who suffered from cerebral ischaemia. In addition we discuss the clinical implications and remaining questions.

## EVIDENCE FROM CLINICAL TRIALS

A large multicentre secondary prevention trial, the European Atrial Fibrillation Trial (EAFT), was published in 1993.<sup>15</sup> In this study, 1,007 NRAF patients with a TIA or minor stroke within the preceding three months were randomised to open treatment with anticoagulants (target INR 2.5-4.0) or double-blind treatment with 300 mg aspirin or placebo (group 1; n=669). Patients with contraindications to anticoagulants were randomised to aspirin or placebo (group 2; n=338). The primary measure of outcome was the composite event of vascular death, nonfatal stroke, nonfatal myocardial infarction or systemic embolism, whichever occurred first. During a mean follow-up of 2.3 years, the annual rate of primary outcome events was 8% in patients assigned to anticoagulants versus 17% in placebo-treated patients of group 1 (hazard ratio [HR] 0.53, 95% CI 0.36-0.79). The risk of stroke alone was reduced from 12%

to 4% per year (HR 0.34; 95% CI 0.20-0.57). In absolute terms: 90 vascular events (mainly strokes) are prevented if 1,000 patients are treated with AC for one year. These findings are remarkably similar to those of the primary prevention studies.<sup>10-14</sup> The most important difference is the much higher absolute risk of subsequent stroke. Among all aspirin treated patients (groups 1 and 2 combined), the annual incidence of primary outcome events was 15%, against 19% in those on placebo (HR 0.83; 95% CI 0.65-1.05). Anticoagulants were significantly more effective than aspirin (HR 0.60; 95% CI 0.41-0.87). The aggregate results of all three AF trials<sup>10,11,15</sup> which directly compared aspirin with placebo show that the effect of aspirin is statistically significant, but is considerably smaller than that of anticoagulants (unpublished data from the Atrial Fibrillation Investigators database). Aspirin prevents about 50 vascular events (of all types) per 1,000 patients treated for one year. The incidence of bleeding events in the EAFT was low, both on anticoagulation (2.8% yearly) and on aspirin (0.9% yearly). No intracranial bleeds were identified in patients using anticoagulation. In a secondary analysis of EAFT data, the optimal level of anticoagulation was found to be INR 2.0 - 4.0.<sup>19</sup> No treatment effect was found below INR 2.0 and most bleedings occurred at INR above 5.0. These findings are in keeping with those of a recent case control study which showed that below INR 2.0 the risk of ischaemic events rapidly increased, and that above INR 3.0 no further benefit was obtained while the risk of bleeding sharply increased at INR 4.0 and above.<sup>20</sup>

In a subgroup of the VA-SPINAF study, 46 patients with atrial fibrillation and cerebral ischaemia were randomised between anticoagulation (INR 1.4-2.8) and placebo.<sup>14</sup> Two ischaemic strokes occurred in the anticoagulation group and four with placebo; the resulting relative risk was 0.66 (95% confidence interval 0.12 to 3.60).

More recently, the results of the Studio Italiano Fibrillazione Atriale (SIFA) were published. In this multicentre, randomised study, 916 patients with NRAF and recent (<15 days) minor stroke or TIA were treated with indobufen 200 mg twice daily or warfarin (INR 2.0-3.5) during 12 months.<sup>16</sup> The incidence of any vascular event was 10.6% in the indobufen group versus 9.0% in the warfarin group (not statistically significant), and that of any stroke 5% and 4%, respectively (not significant). The incidence of major bleeding complications was very low in both groups: in the warfarin group, four intracerebral haemorrhages (0.9%/year) and four major systemic bleeds (1.4%) occurred. These interesting findings, which need to be confirmed in another trial, suggest that indobufen is a valuable alternative in case anticoagulants are contraindicated, and may be more efficacious than aspirin.

SPAF-3 was a randomised clinical trial in 1,044 patients with atrial fibrillation and at least one thromboembolic risk factor.<sup>18</sup> Thirty-six percent had had a previous stroke or TIA, thus this trial may be considered as a partly secondary

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prevention trial. Patients were allocated to either adjusted dose warfarin (INR target 2.0-3.0) or fixed dose warfarin (INR 1.2-1.5) together with aspirin (325 mg daily). The trial was stopped early after a follow-up of 1.1 years. There were 11 ischaemic strokes in the adjusted dose warfarin group and 43 plus one systemic embolus in the combination therapy group. The corresponding relative risk reduction was 75% (95% confidence interval 52 to 87%). The rates of major bleeding were similar in both treatment groups.

#### WHEN TO START

The above studies do not definitively answer the question when antithrombotic treatment should be started after a cerebral ischaemic event in a patient with atrial fibrillation since in both trials a minority of patients were randomised within two weeks after onset of neurological symptoms. Given the high efficacy of anticoagulation it may be that treatment should be started as soon as possible. However, several studies have recommended withholding anticoagulants during the first few days after suspected cardiogenic emboli to the brain, especially in patients with large infarcts.<sup>21,22</sup> Very recently, the results of a large trial in patients with acute stroke, the International Stroke Trial, have been published.<sup>17</sup> In this study, 19,435 patients were randomised within 48 hours of onset, to treatment during 14 days with aspirin alone, 5,000 U or 12,500 U standard unfractionated heparin twice daily subcutaneously, the combination of either dose of heparin and aspirin, or neither. A total of 3,153 patients, or 16%, were in AF. Of AF patients treated with heparin, 44 suffered a recurrent ischaemic stroke versus 79 of those not receiving heparin. However, recurrent haemorrhagic stroke occurred in 32 patients on heparin versus seven in those without. The benefit of heparin regarding the prevention of ischaemic events was therefore completely offset by bleeding complications. In aspirin-treated patients, the number of ischaemic and haemorrhagic stroke were 53 and 22 respectively, versus 70 and 17 in those without aspirin. This difference was not statistically significant. In conclusion, the IST results show that in AF patients with large acute ischaemic stroke early treatment with subcutaneous heparin is neither beneficial, nor harmful within the first 14 days, while aspirin had a small, but non-significant effect.

#### CLINICAL IMPLICATIONS

The findings of primary prevention studies imply that anticoagulation with a target intensity of INR 2.0-3.0 is the therapy of first choice in AF patients with clinical risk factors (age over 75, previous thromboembolism, history of hypertension, or diabetes), or with echocardiographic evidence of impaired left ventricular function.<sup>23</sup> SPAF-3 confirmed these results convincingly.<sup>18</sup> Aspirin can be given to patients with contraindications for anticoagulants.

The optimal treatment for secondary prevention of thromboembolic complications in patients with non-rheumatic atrial fibrillation and a recent TIA or minor ischaemic stroke is oral anticoagulation with an intensity of INR 2.0-3.0. In case of a contraindication to AC, aspirin and ibuprofen are safe, but less effective, alternatives. During the first two weeks following AF-related major stroke, the benefit of subcutaneous heparin is offset by a higher risk of secondary cerebral bleeding, and therefore cannot be recommended at present during that period.

#### REMAINING QUESTIONS

The International Stroke Trial has shown that early heparin in AF patients with major stroke is associated with an unacceptable risk of bleeding complications. The timing of the secondary bleeding complications is yet unknown, however, and it is therefore unknown when it is safe to start. Furthermore, although still not investigated specifically, it seems very probable that massive strokes were particularly prone to haemorrhagic transformation. The risk of early haemorrhage in patients with TIA or minor stroke is probably much lower and these patients can therefore be anticoagulated immediately. This issue has to be sorted out in the near future.

It is unknown how long antithrombotic treatment should be continued. Survival curves from EAFT dispel the common notion that the risk of recurrent events is confined to the early period after the initial event. Both risk and benefit of treatment remained fairly constant during the relatively short period of follow-up (mean follow-up 2.3 years). In the primary prevention studies a previous thromboembolic event was identified as an important risk factor for thromboembolic complications, even if it had occurred years before. Thus, the available data suggest that both anticoagulant and aspirin treatment should be given for as long as possible; that is, until a contraindication or a serious bleeding complication occurs.

Another important question is whether the results of clinical trials discussed above also apply to patients of 80 years or more.<sup>24</sup> Although the mean age in the EAFT was 71 years, there were only 79 patients of 80 years or over. This subgroup is definitely too small for a reliable subgroup analysis, apart from general objections one may have against such analyses. The combined evidence of all clinical trials in AF patients does not suggest a substantial difference in efficacy of anticoagulants in patients under or over 75 years.<sup>25</sup> However, also if anticoagulants are equally effective in preventing embolic stroke in both age groups, it may be much more difficult to improve the very elderly's quality of life since this would require the prevention of falls, arthritis, dementia and many other diseases as well. Data from the EAFT show that increasing age is indeed an independent risk factor for thromboembolic events. This finding is in keeping with the results of the pooled analysis of five primary prevention trials in AF patients.<sup>25</sup> However, we need more data on the efficacy of anticoagulation in fibrillating elderly stroke patients since the lack of precision makes the prescription of anticoagulants in these patients a persisting dilemma.

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## ABSTRACTS OF ORAL PRESENTATIONS

### **Session One - Maintaining Sinus Rhythm**

#### **How Do We Maintain Sinus Rhythm in Paroxysmal Atrial Fibrillation?**

*AJ Camm, JEP Waktare, Cardiological Sciences, St George's Hospital Medical School, London.*

Paroxysmal atrial fibrillation (AF) is a common arrhythmia, but the evidence base for treatment is weak; trials are small, uncontrolled, poorly designed, and have non-standardised endpoints. Despite this, several recommendations can be made. Patients often overestimate the potential morbidity from the disorder, fearing they will suffer a 'heart attack' and clear explanation of the condition to the patient is important.

Several antiarrhythmic drugs have enough supportive data to allow their recommendation, including flecainide, propafenone and sotalol. Worthwhile reduction in AF episode frequency without therapy limiting side effects can be expected in 50 to 90% of patients. Propafenone and flecainide both have low side effect profiles, and are attractive first line agents for 'lone' AF patients. Comparative data is restricted, and the response of individuals to an agent can not be predicted, so serial therapy until effective control is achieved is required. Amiodarone use is to date only supported by un-controlled studies, but none-the-less appears highly effective. Its side effect profile precludes its widespread first line use, although this is appropriate in some sub-groups (e.g. patients with heart failure). It may be effective in those who have failed other agents, and has also been employed in special situations such as following cardiac surgery. A role for autonomic tone in initiating AF and the use of vagolytic drugs (e.g. disopyramide) or atrial pacing in those with parasympathetically triggered AF is suggested. While systematic data supporting this is largely absent, the broader principle of identifying and modifying triggering events is sometimes useful. Pro-arrhythmia is of concern with all agents, and can take the form of heart block, ventricular arrhythmias (including torsades des pointes), and rapid ventricular rates due to atrial flutter. Careful pre-treatment assessment and appropriate follow-up monitoring with ECG and Holter are vital.

Antiarrhythmic drug therapy therefore offers effective therapy for a large number of patients, but disease control is often not complete. For those where acceptable symptom reduction is not possible, promising non-pharmacological therapies are emerging, to be employed alone or, as with atrial pacing with drug therapy, employed in combination.

#### **Why Digoxin is Not the Answer**

*K Jennings, Cardiology, The Royal Infirmary, Aberdeen.*

Atrial fibrillation(AF) is common and its consequences are potentially significant; because of the heterogeneity of patients with AF, treatment strategies are likely to differ. For some restoration and maintenance of sinus rhythm (SR) is desirable, while for others control of ventricular rate and anticoagulation may be more appropriate. Heart rates increase during exercise because of high sympathetic tone and rapid irregular rates decrease cardiac output and therefore exercise tolerance. Restoration of SR achieves improvement in LV function, exercise capacity and stroke volume index. The mechanism by which digoxin alters AV nodal conduction is largely attributable to modulation of the autonomic nervous system, primarily through increased vagal tone. Digoxin is effective in reducing resting ventricular rate in

established AF; when sympathetic tone is increased (as in exercise) it is largely ineffective in rate control. It is not effective in preventing rapid rates in paroxysmal AF, nor in preventing relapses. Both beta and calcium channel blocking agents are effective in rate control in chronic AF both at rest and on exertion. At toxic doses digoxin can be associated with increased automaticity increasing likelihood of arrhythmias. Altered levels of potassium, magnesium and calcium increase the likelihood of arrhythmias with digoxin. Patients with acute haemodynamic deterioration due to AF should be considered for electrical cardioversion; in less acute situations antiarrhythmic agents may be used; control of ventricular rate can be achieved with IV beta or calcium channel blocking agents. Digoxin is less useful in the acute situation because of delayed onset of action and lack of efficacy in situations of increased autonomic tone.

Digoxin is not effective in converting AF to SR; benefit has been shown with quinidine, procainamide, propafenone, flecainide, sotalol and amiodarone; placebo-controlled studies have shown that only about 25% of patients receiving placebo remain in SR one year after successful cardioversion. All of the above-mentioned agents have been shown to be more effective than placebo in maintaining SR with one year rates of 40-60%.

**In conclusion:** digoxin is not effective in controlling heart rate in presence of high sympathetic tone; it does not cardiovert patients with AF to SR, maintain SR in patients with paroxysmal AF nor control the ventricular rate of paroxysmal AF when used prophylactically.

#### **Non-pharmacological Approaches to Atrial Fibrillation**

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Most of the goals of treating atrial fibrillation (AF) can be achieved by non-pharmacological means which have traditionally been reserved for patients refractory to pharmacological therapies. External cardioversion is a tried and trusted method of restoring sinus rhythm (SR) from established AF, most useful in patients with infrequent episodes of AF of prolonged duration. Other non-pharmacological approaches can be divided into implantable device therapies, catheter ablation and surgical therapies.

**The devices** used are either pacemakers with atrial sensing and pacing capability or implantable defibrillators. Pacemakers are effective in preventing AF in patients with sino-atrial disease where AF is triggered by sinus bradycardia or pauses. Newer, more sophisticated pacing approaches seek to co-ordinate atrial activation by pacing from two atrial sites whereas the defibrillator can identify the onset of AF and then deliver an R wave synchronised shock to restore SR. These modalities are currently under investigation in patients with troublesome paroxysmal AF.

**Catheter ablation** in man was initially restricted to destroying the AV node of drug refractory AF patients but has evolved to be applied to almost every arrhythmia. For AF, existing catheter techniques are successful in eliminating identifiable triggers to AF such as accessory pathways and increasingly to focal sources of AF located within veins draining into the atria. The elimination of AF in most patients remains a difficult target. The most successful non-pharmacological approach has been the **surgical Maze procedure** where the atria are systematically divided and repaired so that the healed incisions form a maze like barrier to the formation of AF, protecting sinus nodal control of atrial activation and directing it to the AV node. To readily reproduce this by

catheter techniques is a holy grail and requires newly developed linear catheters now entering clinical trials.

## **Session Two - Restoring Sinus Rhythm**

### **Overview of Cardioversion Trials**

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Atrial fibrillation occurs in a wide variety of clinical circumstances. There is a relatively high spontaneous rate of reversion to sinus rhythm, especially when the duration of atrial fibrillation is short. Attempts to convert atrial fibrillation are most likely to be successful when the duration of the arrhythmia is short, and the heart is not enlarged. Clinical trials with different methods of converting atrial fibrillation to sinus rhythm are generally small, and of poor quality. DC cardioversion has never been subjected to a randomized trial, but it appears the most effective method of restoring sinus rhythm. The main disadvantage is the need for general anaesthesia. Digoxin is certainly of no value for converting atrial fibrillation, and Verapamil is probably equally ineffective. Of the Class I anti-arrhythmic agents, such evidence as there is suggests that Flecainide is the most effective.

### **Cardioversion for Atrial Fibrillation: Is It Worth the Energy?**

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It is a well known fact that atrial fibrillation is a chronic disease. This holds for all types of fibrillation, i.e. paroxysmal, persistent and permanent atrial fibrillation. By definition, in permanent atrial fibrillation there is no role for cardioversion. On the other hand, in paroxysmal atrial fibrillation sinus rhythm is the ultimate goal of treatment and cardioversion is always worth the energy. Obviously cardioversion is appropriate only in prolonged attacks of paroxysmal atrial fibrillation, e.g. terminating only after a few days. This type of paroxysmal atrial fibrillation is likely to degenerate into persistent atrial fibrillation. Apart from prevention of persistent atrial fibrillation, cardioversion is worth the energy in these patients because of usually severe complaints. As yet there is no definite answer to the question whether simple rate control during attacks is as good as or even better than a strategy aiming at restoring sinus rhythm at each attack and maintaining the rhythm thereafter. To answer this question, the results of the AFFIRM study have to be awaited. Cardioversion is mostly applied in persistent atrial fibrillation. It is especially a rewarding procedure if chronic sinus rhythm is warranted and feasible. However, it is well known that after cardioversion most patients will have a recurrence and it is clear that repeated cardioversions are necessary to obtain chronic sinus rhythm. Drawbacks of the cardioversion strategy are the necessity of repeated cardioversions and hospitalisations and side effects of the inevitable class I or class III antiarrhythmic drugs. On the other hand, if sinus rhythm can be maintained the advantages are considerable. First of all, there is improvement of left ventricular function and prevention of heart failure. Left atrial size decreases and atrial kick is restored. In addition, cardiac output is increased acutely after cardioversion. In the long term exercise tolerance is maintained in patients maintaining sinus rhythm whereas it decreases more than expected in those with ongoing atrial fibrillation. The question remains however whether complaints and thromboembolic complications are reduced during a cardioversion strategy. These answers may come from the RACE and PIAF studies.

### **Reducing the Thromboembolic Risk of Cardioversion**

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Cardioversion to sinus rhythm should be considered for all patients in atrial fibrillation (AF) in order to improve cardiac performance and perhaps to reduce the long-term risk of thromboembolic complications. Anticoagulant therapy begun before, and continued following cardioversion is advised although the most effective

anticoagulation regime (and duration of therapy) still remains uncertain. The risk of thromboembolism probably continues despite successful cardioversion as atrial mechanical function may not be restored for several weeks. Recent recommendations suggest the following (i) the administration of anticoagulation (INR 2.0-3.0) for 3 weeks before elective cardioversion of AF of  $\leq 2$  days' duration; (ii) continuation of warfarin therapy for 4 weeks after cardioversion; and (iii) administration of intravenous heparin followed by warfarin if cardioversion cannot be postponed for 3 weeks. However, in patients who have a high risk of recurrent AF, it may be prudent to continue anticoagulation for longer than 4 weeks. Transoesophageal echocardiography (TOE) may help in reducing the thromboembolic risk of cardioversion, as it is superior to transthoracic echocardiography in detecting atrial thrombi. However, the exclusion by TOE of pre-existing thrombi before cardioversion does not eliminate the risk of thromboembolism, as post-cardioversion atrial dysfunction or 'stunning' still promotes thrombogenesis. TOE would probably be a useful investigation in patients in whom anticoagulation is especially hazardous; the role for TOE should be to enable early cardioversion if atrial thrombus is excluded and to identify high risk patients with atrial thrombi, so as to postpone cardioversion and minimise any risks of thromboembolism. Strategies to maintain sinus rhythm long-term, including antiarrhythmic drugs, may reduce thromboembolic risk, but results of randomised trials are still awaited.

## **Session Three - Achieving Optimal Cardiovascular Function**

### **Rate Control in Atrial Fibrillation: How Do We Achieve Optimal Cardiovascular Function?**

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*Background paper by RWF Campbell, Academic Cardiology, Freeman Hospital, Newcastle upon Tyne, England*

Atrial fibrillation (AF) has a haemodynamic cost compared to sinus rhythm. The haemodynamic detriment of AF is principally related to inappropriate rate response, combined with lack of atrial systole and cycle length irregularity. Control of the ventricular response rate in AF is necessary to achieve the aim of improved cardiac function but optimal rate control is not well defined. Digoxin monotherapy has been traditionally used and effectively controls resting heart rate but offers poor control of exercise rate. Combinations of digoxin with beta blockers or calcium antagonists may improve rate control but evidence of improved cardiac function or increased effort capacity is scant. Radiofrequency (RF) ablation of the AV node with rate responsive pacing offers the best control of rate. There is evidence of both symptomatic and objective functional benefit. Cost, availability and a concern about late sudden death has limited AV node ablation to those who fail or do not tolerate drug therapy. RF modification of the AV node may control rate in AF without requiring pacing, but more studies are needed. Continued efforts are required to achieve appropriate rate control in individual patients with AF in order to optimise cardiovascular function.

## **Session Four - Preventing Thromboembolism in Atrial Fibrillation**

### **Overview of Primary Prevention of Thromboembolism in Atrial Fibrillation**

**R Hart**, *O Benavente, University of Texas Health Science Center, San Antonio, Texas, USA.*

**Background:** Nonvalvular atrial fibrillation (AF) is an independent risk factor for stroke; about one in six ischemic strokes is associated with AF.

**Objectives:** To review strategies for the primary prevention of stroke in AF patients, considering the benefits and risks of

interventions in specific patient subgroups.

**Methods:** Review of the literature, including 10 randomized trials of antithrombotic therapy as well as longitudinal cohort studies addressing thromboembolic risk stratification.

**Main Results:** The overall risk of ischemic stroke in AF patients without prior stroke averages about 5%/yr, but with wide variation depending on the presence of coexistent thromboembolic risk factors. AF patients with low (about 1% per year), moderate (2-4% per year) and high (about 6% per year) stroke risks have been identified, but the generalizability of available risk stratification schemes to clinical practice has not been fully defined. AF patients with prior stroke or transient ischemic attack (i.e. secondary prevention) are at highest risk (about 12% per year). Adjusted-dose warfarin (target INR 2-3) is highly efficacious for primary prevention of stroke in AF patients (about 70% risk reduction) and is relatively safe for selected patients, if carefully monitored. Aspirin has a modest effect on reducing stroke (about 25% risk reduction for primary prevention). The number of ischemic strokes saved by using warfarin instead of aspirin per 1,000 AF patients so treated is about 5, 18 and 45 for those at low, moderate and high risk, respectively.

**Conclusions:** Warfarin therapy should be considered for AF patients predicted to have a high risk of stroke and who can safely receive it. Aspirin may be indicated for AF patients at low risk for stroke and for those who cannot safely receive adjusted-dose warfarin. For those with moderate stroke risk, individual bleeding risks during anticoagulation and patient preferences should guide antithrombotic therapy. Additional studies to further refine risk stratification schemes and assess their reliability are needed.

### Overview of Secondary Prevention of Thromboembolism in Atrial Fibrillation

**A Algra, A Koudstaal, PJ Koudstaal.** Departments of Neurology, University Hospitals Utrecht and Rotterdam, the Netherlands.

Patients with non-rheumatic atrial fibrillation (NRAF) who have suffered a transient ischaemic attack or minor ischaemic stroke have an annual risk of stroke recurrence of 12%; the annual mortality rate is 5%. Two trials (N=1923) addressed the efficacy of antithrombotic treatment after an attack of cerebral ischaemia and one trial (N=1044) in high risk patients of whom 36% had had cerebral ischaemia. Anticoagulant treatment with an intensity of INR 2.0-3.0 was more efficacious than no treatment (relative risk (RR) for vascular events 0.53; 95% confidence interval (CI) 0.36-0.79), than 300 mg aspirin per day (RR 0.60; 95% CI 0.41-0.87) or than the combination of fixed dose anticoagulation (INR 1.2-1.5) plus 325 mg aspirin daily (RR 0.25; 95% CI 0.13-0.48). There were no major differences in the efficacy of anticoagulation (INR 2.0-3.5) and indobufen (2 x 200 mg daily). The optimal level of anticoagulation was found to be INR 2.0-4.0 in one trial. Aspirin reduced the risk of vascular events by 17% (95% CI -5%, 35%) in comparison to placebo.

**In conclusion:** anticoagulants (INR (2.0-3.0) should be given to patients with NRAF and recent cerebral ischaemia. If there is a contraindication to such treatment aspirin or indobufen may be used as an alternative.

### How do We Prevent Thromboembolism in Atrial Fibrillation? The Cardiologist's Viewpoint.

**P Bloomfield.** Royal Infirmary of Edinburgh

The Cardiologist's role is in providing optimal treatment for those with paroxysmal atrial fibrillation in reducing the frequency of attacks and preventing the development of established atrial fibrillation. We aim to provide prompt and ready assessment of those who have developed AF with a service for electrical or chemical cardioversion with minimal delay. In a small minority of patients early specific treatment may prevent AF, e.g. in those with mitral valve regurgitation pursuing early surgery for valve repair.

The Cardiologist can aid the risk stratification of patients with AF; the most important tools of a history, physical examination,

ECG, and chest X-ray will identify the vast majority of patients at high risk of systemic embolism and are available to all physicians. Echocardiography will identify a few additional patients with genuinely occult valvular heart disease, mitral annular calcification, or marked enlargement of the left atrium who may be at increased risk. The most important echocardiographic risk factor, i.e. left ventricular dysfunction can usually also be identified by clinical assessment; analysis of trial data has shown it to be an important risk factor for the development of systemic embolism.

The Cardiologist must liaise with colleagues in General Practice and Geriatric Medicine who will see the vast majority of patients with AF, a condition of the elderly; the decision to anticoagulate must be a joint one to balance the risks with the benefits.

### Atrial Fibrillation - The Neurologist's Viewpoint

**P Humphrey.** Walton Centre for Neurosciences, Liverpool, United Kingdom.

Anticoagulation is not recommended for TIAs or non haemorrhagic strokes in general following the Spirit Study in which INRs of 3 - 4.5 were used. However, patients in atrial fibrillation (AF) are more likely to suffer an embolic stroke than those in sinus rhythm. Furthermore strokes after AF are usually more severe with a higher mortality than those in general. Patients in AF are 2-3 times more likely to suffer a cortical infarct which tend to be embolic and 2-3 times less likely to have small deep lacunar infarcts which are usually secondary to local small deep vessel disease. Following a recent TIA ischaemic stroke there is little doubt from the secondary prevention trials that anticoagulation is the treatment of choice. In general 15% of strokes are due to haemorrhage. Approximately 10% of patients with haemorrhagic stroke have AF. It is clear, therefore, that CT scanning to exclude haemorrhage is necessary before considering anticoagulation.

There is much debate about when to start treatment. The International Stroke Trial and Oxford Community Stroke Trial suggest that the risk of a subsequent stroke in those with atrial fibrillation in the first 2-4 weeks after the initial stroke is very low (1%). The recent consensus statement on stroke published by the Royal College of Physicians of Edinburgh states that immediate anticoagulation is not necessary; it can be delayed for two weeks. In the rare instance that immediate anticoagulation is deemed necessary, then the cerebral embolism task force suggests that immediate anticoagulation is safe, with minimal risk of secondary intracerebral haemorrhage, if the neurological deficit is mild and/or the infarct on CT is small.

The risk of stroke in AF is associated with increasing age, co-existing ischaemic heart disease, previous clinical or CT evidence of thromboembolism, systolic BP > 160 mmHg, non-rheumatic AF of more than one years duration, enlarged cardiothoracic ratio on CXR. The more risk factors the higher the risk of stroke.

INRs of 2.0 - 3.0 seem to offer maximal protection with least risk. The risk of haemorrhagic complications is greatest in those with INRs of more than 4, co-existing diabetes mellitus, antiplatelet treatment, uncontrolled hypertension or leukoariorosis (increased periventricular white matter signal on CT or MRI). How easily these different risks can be applied to those over 80 years of age where atrial fibrillation is most common is difficult to assess. Much of the data applies to a younger age group.

### Atrial Fibrillation - The Geriatrician's Viewpoint

**RI Lindley.** SJ Brennan, RA Manson. Royal Victoria Hospital, Edinburgh.

Atrial fibrillation (AF) is a very common transient problem affecting the acutely ill elderly patient admitted to hospital. The diagnosis and subsequent search and treatment for underlying causes of AF are no different in older people. The geriatrician's troubles arise from two main methodological problems:

- 1) Too few elderly have been randomised in the randomised controlled trials (RCT).
- 2) The types of older person in the RCT's are dissimilar to the frail patients we see in geriatric medicine.

These problems give rise to imprecision in our knowledge of treatment effects in the old and limited generalisability for our patients. For example, in a recent audit of all the in-patients in a specialised geriatric and psychogeriatric hospital in Edinburgh (the Royal Victoria Hospital), 27/225 (12%) patients were in atrial fibrillation. However, only 2 (7%) of these 27 were warfarinised, 13 (48%) were on aspirin and 12 (44%) were on no antithrombotic prophylaxis. Only a few of the untreated patients had no clear contra-indications to aspirin or warfarin.

When considering warfarin treatment in the elderly it is essential to check cognition, dexterity, vision, previous compliance with medication, the tendency for falls, alcohol history and the patients' preference ('a better treatment which needs regular blood tests and frequent changes in dosage or a less powerful treatment which is simply one tablet a day').

### **Atrial Fibrillation - The General Practitioner's Viewpoint**

**C Burton**, General Practitioner, Sanquhar.

#### **Similarities and differences between Primary Care and the research environment**

Practice populations of patients with AF contain a wider case mix than those selected for rigorous research studies; they also contain many 'typical' study patients. Case finding strategies for use in primary care will not identify all patients with AF but information within practices appears adequate to assess stroke risk. The effectiveness of warfarin control in primary care is an area of increasing clinical interest and appears to be comparable to outpatient anticoagulation in terms of control achieved. However there have not been meaningful primary care outcome/complication studies and these are now needed.

#### **Obstacles to change - physician attitudes and resources**

Physicians inevitably adopt new treatments and attitudes at different rates and early information is often perceived as confusing and conflicting. For many in primary care warfarin treatment for AF is either a 'new' treatment on which the jury is still out, or a complex issue best left alone for now.

Anticoagulation carries, for many practices, additional workload and responsibility which is not specifically remunerated. For patients too, anticoagulation carries considerable inconvenience and for many of them specific arrangements need to be made to provide reasonable access. If anticoagulation for patients with AF is to be a priority, commissioning organisations need to address resources.

#### **Patient values and perception of risk**

Patients making decisions about treatment with warfarin, particularly when they perceive themselves as well, face real and difficult choices. Individuals' perception of risk, notions of what disability would mean to them and risk-taking behaviour all differ, but need to be taken into account.

## **Session Six - GP:Hospital Interface**

### **Prevalence and Identification of Atrial Fibrillation in the Community**

**RA Kenny**, M Sudlow, School of Clinical Sciences, University of Newcastle upon Tyne, United Kingdom.

**Background:** The resource implications of recent demonstration of the effectiveness of anticoagulants in preventing stroke in atrial fibrillation and flutter (AF) remain unknown, but will be important in implementing these findings in practice. This study was designed to determine the prevalence of AF in the UK and to estimate what proportion of patients with AF might benefit from anticoagulation.

**Methods:** A random community sample of 4,843 subjects aged

65 and over were screened for AF with electrocardiograms. Subjects with AF were further investigated to identify risk factors for stroke and contraindications to anticoagulants and to predict whether they would benefit from anticoagulants.

**Findings:** The prevalence of AF in those aged 65 and over was 4.7%. A high proportion of those with AF would benefit from anticoagulation according to analyses derived from risk stratifications based on the Stroke Prevention in Atrial Fibrillation study (61%) or pooled analysis of trial results (49%), and from the inclusion criteria for the Stroke Prevention in Atrial Fibrillation 3 study (41%). In the present sample anticoagulants were used by 23%, and were least used in elderly females, who may be most likely to benefit. Echocardiography would provide useful information in assessing the need for anticoagulation in only a small proportion of subjects.

**Interpretation:** AF is as prevalent in the UK as in other developed countries. The risk of stroke in community subjects with AF is high according to several risk stratification schemes, and the majority of patients with AF would probably benefit from anticoagulation. Echocardiography rarely contributes to decisions about anticoagulation. Anticoagulants appear to be underused and misdirected according to a variety of criteria. Efforts to promote and support wider and more appropriate use of anticoagulants appear to be justified, and should be rewarded by a substantial reduction in stroke incidence amongst these patients. Such expansion of the use of anticoagulants could prevent an additional 3,000 to 5,000 strokes in Great Britain annually.

### **Anticoagulation Control in General Practice**

**BM Goudie**, Dundee.

Monitoring of oral anticoagulant therapy has traditionally been undertaken in hospital anticoagulant clinics, or in general practice where venous blood samples have been sent to hospital laboratories for testing.

Portable analysers are now available which allow near patient testing (NPT) of the international normalised ratio (INR). However, it is necessary to ensure compatibility between NPT and hospital analysers, and uniform quality control standards must be applied in primary and secondary care. Warfarin dosage may be determined by clinical judgement, written protocols, or computer decision support systems. INR testing and warfarin dosing has been successfully performed by pharmacists, nurses and patients themselves.

Cost per consultation (testing and dosing) is highly sensitive to patient throughput; short consultation time and high test rate equating with lower cost. Total service costs are, in addition, dependent on retest interval which may be influenced by level of staff expertise and the dosing protocol.

Opinion varies among primary care professionals. Some support the development of NPT and others, who express concern about issues such as workload, inadequate resources and lack of expertise, are reluctant to take on additional responsibility for monitoring anticoagulant therapy.

There should be a flexible approach to service development. Convenient high quality anticoagulant therapy can be provided in primary care using a variety of NPT based models and this will be the optimum setting in certain circumstances. Common quality standards must be determined for all anticoagulant services in key areas, such as staff training, INR testing, dosage advice, record keeping, patient information and performance review. The equitable provision of these services has significant funding implications for the NHS.

### **Should All Patients With Atrial Fibrillation be Assessed by a Cardiologist?**

#### **Proposing Presentation**

**FG Dunn**, Stobhill Hospital, Glasgow, United Kingdom.

#### **Opposing Presentation:**

**R Hobbs**, Department of General Practice, University of Birmingham, United Kingdom.

**Session Seven - New Aspects of Atrial Fibrillation**

**Atrial Fibrillation Begets Atrial Fibrillation**

**C Garratt**, Manchester Heart Centre, Manchester, United Kingdom.

In 1995, Maurits Allesie produced experimental evidence to show that atrial fibrillation has self-perpetuating properties and that sustained episodes of this arrhythmia result in changes in atrial electrophysiology (atrial electrical remodelling) that make reinduction or maintenance of the arrhythmia more likely. Since that time a number of different animal studies have confirmed the self-perpetuating properties of atrial fibrillation. A number of clinical hypotheses arise from these observations.

- 1) the frequently-observed clinical progression of paroxysmal to chronic AF may be avoided by aggressive antiarrhythmic therapies as opposed to being an inevitable consequence of the natural history of an underlying disease.
- 2) early recurrence of persistent AF post-cardioversion does not necessarily mean that the atrium cannot maintain sinus rhythm in the long-term.
- 3) suppression of the atrial remodelling process itself may have important antiarrhythmic properties.

These hypotheses are currently under test.

**New Antithrombotic Regimens**

**AGG Turpie**, McMaster University, Hamilton, Canada.

Antithrombotic therapy with oral anticoagulants (a/c) or aspirin (ASA) for the prevention of stroke in atrial fibrillation (AF) is based on several recent randomized clinical trials. Improved monitoring and dosing regimens of oral a/c has greatly improved their efficacy and safety, but the risk of bleeding remains a significant issue. ASA has a number of limitations including a relatively low risk reduction in stroke compared with oral a/c. The combination of ASA with low-dose a/c has proved ineffective compared with oral a/c adjusted to a target INR of 2.0-3.0. Several new anticoagulants have been developed including low molecular weight heparins (LMWH), heparinoids and direct thrombin inhibitors. A LMWH, nadroparin, has been shown to provide the same risk reduction in stroke as oral a/c in patients with AF who were intolerant to oral a/c. LMWH may be used when oral a/c are temporarily discontinued in high risk patients. A number of orally active direct thrombin inhibitors are under development and may be alternatives to oral a/c. Aspirin is the only antiplatelet drug recommended in AF but its effects are only modest. Several new antiplatelet drugs are now available. The thienopyridine agents, ticlopidine and clopidogrel that block ADP-induced aggregation have been shown to be more effective than aspirin in patients at risk of vascular events. Glycoprotein IIb/IIIa receptor blockers including the monoclonal antibody abciximab, the peptide inhibitor, eptifibatide and the non-peptide inhibitors tirofiban and lamifiban have been developed and shown to be effective following coronary revascularization and in patients with unstable angina. Oral glycoprotein IIb/IIIa receptor blockers are in development. The new antiplatelet drugs have yet to be tested in AF.

**A National Anticoagulation Service - Should We Go**

**Dutch?**

**F van den Meer**, Leiden University Medical Centre, The Netherlands.

In The Netherlands outpatient anticoagulant therapy is monitored by anticoagulation clinics. These clinics exist already more than 40 years and are regionally organized. All patients in a certain area visit the same clinic, irrespective of the referring physician. Nurses who are specially trained in anticoagulant therapy control play a central role. They collect blood samples of the patients at outpatient facilities or when necessary patients are visited at home. With every venepuncture a standardized short history is taken about bleeding complications, changes in co-medication, intercurrent illnesses and surgical procedures. Each new patient receives extensive instructions about anticoagulant therapy. Subsequently, prothrombin times (INRs) are assessed at the anticoagulation clinic where a team of specialized physicians determines the dosage and the control period. The dosage is printed on a dosage list which the patient receives by mail the next day. In case of bleeding complications or excessive intensity of the anticoagulant effect the patient is phoned the same day for dose adjustment or administration of vitamin K.

There are 68 anticoagulant services in The Netherlands, which are organised in the Dutch Federation of Thrombosis Services. This Federation sets guidelines for treatment, facilitates laboratory control, organises external quality assessment programs, organises conferences and postgraduate training, promotes research and publishes its own newsletter. Recently a quality system with audits and accreditation has been introduced. Besides laboratory quality control therapeutic quality control has much attention. Various methods are available to assess therapeutic quality control which is defined as the time patients spent within their therapeutic range. Furthermore, these data can be evaluated in relation to the number of observed bleeding complications (clinical quality control). Yearly all Dutch thrombosis services provide therapeutic and clinical quality control data which are to be included in an annual report by the Federation. In 1996 in The Netherlands a total number of 287,749 patients were treated with oral anticoagulants (one of every 54 inhabitants). Regarding atrial fibrillation an increase in the total number of patients treated for this indication is observed from 41,014 in 1994 to 55,127 in 1996. A target range of INR 2.5-3.5 is used.

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