Drug therapy for the management of atrial fibrillation: an update

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Abstract

With an ageing population in the United Kingdom, atrial fibrillation has become an increasing cause of morbidity and mortality, and a burden on health resources. Drug therapies for the management of atrial fibrillation have a number of roles, including the restoration and maintenance of sinus rhythm and the prevention of thrombo-embolic complications. New anti-arrhythmic drugs are under development and alternatives to warfarin are being investigated. This article examines the current knowledge on the effectiveness of drug therapy in atrial fibrillation and discusses some aspects of the future of drug therapy for atrial fibrillation.

Key words: atrial fibrillation, drug therapy.

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Introduction

Atrial fibrillation (AF) is becoming an increasingly common condition and, with an ageing population, the arrhythmia is a significant cause of hospital admission, morbidity and mortality.[1,2] The median age of patients with AF is 75 years and 84% are older than 65.[3] Drug therapies for the management of AF have a number of important roles, including: maintaining sinus rhythm in patients with paroxysmal AF, the control of ventricular rate in persistent AF, chemical cardioversion, facilitating electrical cardioversion, preventing recurrence of arrhythmia after cardioversion, and reducing the risk of thrombo-embolic complications.

Prevention of paroxysmal atrial fibrillation

The current European guidelines for the prevention of paroxysmal AF suggest that drug therapy should be patient-tailored depending on the underlying aetiology.[4] Anti-arrhythmics of classes 1A, 1C and III are associated with increased sinus rhythm at follow-up in comparison with placebo.[5] In the absence of structural heart disease, class 1C drugs are believed to be the safest. Patients with vagal-mediated AF may respond to flecainide or disopyramide. Beta blockers should be considered in patients with co-existing coronary artery disease, either amiodarone or dofetilide should be used in patients with heart failure and patients with severe left ventricular hypertrophy should be treated with amiodarone.[6]

Rate or rhythm control?

One of the long-standing uncertainties in AF management has been whether to achieve rate control or rhythm control in patients with persistent AF. The two approaches were compared in the Pharmacological Intervention in Atrial Fibrillation (PIAF) trial, a randomised trial in 252 patients with AF of seven to 360 days' duration.[7] The trial showed that both strategies resulted in similar symptom scores during long-term follow-up but exercise tolerance was improved with rhythm control (at the expense of more frequent hospital admissions).

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial randomised 4,060 elderly patients to medical therapy to either restore atrial rhythm or to control ventricular rate.[8] At an average of 3.5 years of follow-up, 60% in the rhythm arm were in sinus rhythm and adequate rate control was achieved in 80% of rate-control patients. The primary end point (total mortality) was unchanged between the two treatment groups, although there was a trend towards more stroke in the

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rhythm control group. Warfarin use at study end was 85–90% in the rate group and 70% in the rhythm group.

The Rate Control *vs.* Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial was presented in the same journal.[9] The investigators compared the strategies of rate control with medical therapy and repeat electrical cardioversion. Over a three-year follow-up period there was no difference in mortality between the 256 patients randomised to rate control and the 266 patients randomised to rhythm control. There were, however, more thrombo-embolic complications in the rhythm group suggesting that anticoagulation therapy may need to be continued for longer in patients with persistent AF.

Ventricular rate control

Sustained high ventricular rates during persistent or permanent AF can lead to a deterioration in left ventricular function.[10-12] Historically, digoxin has been used as the pharmacological agent of choice but it has been shown that digoxin, alone, is inadequate at controlling heart rate during exercise in many patients.[13] Beta blockers or rate controlling calcium antagonists, such as diltiazem or verapamil, are more effective at ventricular rate control.[14-17] Amiodarone has been shown to have some effects at controlling heart rate in AF, possibly via its weak beta-blocking properties, but only when given intravenously.[18,19]

Cardioversion of persistent atrial fibrillation

There are data supporting the use of intravenous flecainide and amiodarone for cardioversion of persistent AF but amiodarone appears to have a delayed time to action.[20-23] Intravenous propafenone has been shown to convert 91% of patients with persistent AF after 2.5 hours.[24] Intravenous ibutilide is currently the most rapid anti-arrhythmic for chemical cardioversion of AF achieving sinus rhythm in 30–50% of episodes and often within 30 minutes of infusion.[25,26] There is, however, the risk of polymorphic ventricular tachycardia in up to 3% of patients. It is not yet licensed for use in the United Kingdom.

Pharmacological cardioversion can also be achieved with oral anti-arrhythmic drugs, particularly class 1 agents, with a low risk of pro-arrhythmia.[27] The 'pill in the pocket' approach has been shown to be successful with either a single dose of propafenone 600 mg or flecainide 300 mg, restoring 50–80% of episodes to sinus rhythm.[28-30]

Facilitation of cardioversion

Electrical cardioversion of persistent AF is successful in 80–90% of patients and this can be increased further by pre-treatment with sotalol, ibutilide or amiodarone.[31-33] These drugs work by reducing the atrial defibrillation threshold and by preventing some of the immediate recurrences of AF.

Prevention of persistent atrial fibrillation recurrence

The relapse rate of AF after cardioversion is extremely high. Li *et al.* reviewed 150 consecutive patients who had no reversible cause of AF.[34] They found that those not prescribed anti-arrhythmic therapy had a significantly higher relapse rate with only 26% remaining in sinus rhythm at one year. The majority of recurrences occur in the first few weeks after cardioversion, probably as a result of atrial remodelling.[35] Some of the remodelling changes that occur in AF are related to changes in the L-type calcium current and calcium handling.[36] It has therefore been suggested that calcium antagonists may have a place at preventing remodelling but results from animal and human models are mixed.[37-41]

Metoprolol has been shown to maintain sinus rhythm after cardioversion, as have both sotalol and propafenone.[42,43] A comparison study suggested no additional advantage of sotalol over bisoprolol after cardioversion and highlighted the inherent risk of pro-arrhythmia with sotalol.[44] Quinidine has been shown to reduce recurrence rates of AF after cardioversion by 50% but a meta-analysis has pointed towards the potential increased mortality with use of this drug.[45]

There has been recent interest in the role of the renin-angiotensin system in atrial electrical remodelling. Inhibition of endogenous angiotensin II by captopril or candesartan prevents the shortening of atrial refractory periods during rapid atrial pacing in dogs.[46] Enalapril prevented the structural and electrical changes that promote AF initiation in an experimental heart failure model.[47] Pedersen *et al*. demonstrated that treatment with the angiotensin-converting enzyme (ACE) inhibitor trandolapril reduced the risk of developing AF after myocardial infarction by 55% during long-term follow-up.[48] This difference could not be explained by differences in levels of potassium or left ventricular function. Patients on ACE inhibitors have also been noted to have an improved outcome from cardioversion.[49] Madrid *et al*. studied 154 patients undergoing cardioversion of persistent AF.[50] Seventy-five patients were randomised to amiodarone only and 79 were randomised to amiodarone plus irbesartan. At two months, 85% of patients were still in sinus rhythm on combination therapy compared with 63% in the amiodarone only group. It is theorised that blockade of angiotensin II prevents atrial electrical remodelling by decreasing atrial stretch, modulating refractoriness, interfering with ion currents, modifying sympathetic tone and stabilising electrolyte concentrations.[46]

Data from the first anti-arrhythmic drug substudy of AFFIRM were published recently.[51] The investigators demonstrated a clear superiority of amiodarone in achieving sinus rhythm at one year compared to all other drug types. In a comparison between amiodarone and class 1 agents in 222 patients, 62% of patients were successfully treated with amiodarone compared with 23% randomised to class 1 agents ($p<0.001$). Similarly, in 256 patients, 60% of patients were successfully treated with amiodarone compared to 39% of those randomised to sotalol ($p=0.001$). There is also evidence suggesting that the use of amiodarone after cardioversion reduces costs by preventing hospitalisations and reducing the need for repeat cardioversion procedures.[52] The side effects associated with the use of amiodarone may, however, reduce the expected benefits in quality of life. Use of low-dose amiodarone (100 mg) may reduce side effects but data on its long-term efficacy remain unknown.[53]

Anticoagulation

A meta-analysis of 16 trials of antithrombotic strategies including 9,874 participants was published in 1999.[54] The investigators concluded that adjusted-dose oral anticoagulation was highly effective at preventing stroke (both ischaemic and haemorrhagic) in patients with AF with a risk reduction of 61% (95% CI, 47% to 71%) *vs.* placebo. Aspirin reduced stroke by 22% (CI, 2% to 38%). The mean follow-up, however, was 1.7 years, which is considerably shorter than the period usually seen in clinical practice. It is also unclear if the low rates of major haemorrhage observed in these carefully managed trials correspond to the older population (whose anticoagulation therapy is often less closely regulated) seen in practice in the UK. Indeed, an analysis of quality adjusted life expectancy and cost in the oldest old has indicated that there remains no evidence that routine anticoagulation in the very elderly is beneficial.[55]

Current guidelines recommend the continuation of anticoagulation for three to four weeks after cardioversion if the arrhythmia episode lasted longer than 48 hours.[4] This is because following conversion of AF to sinus rhythm there is a period of transient mechanical dysfunction of the left atrium and atrial appendage, known as 'stunning'.[56] Due to the high relapse rate after cardioversion it may be more appropriate to continue anticoagulation for a longer period.[57] The differences in stroke rates noted in the AFFIRM study may be as a consequence of the early discontinuation of anticoagulation in the rhythm control group. An approach using transoesophageal echocardiography to exclude left atrial thrombus was shown to reduce the time to cardioversion (three days *vs.* 31 days) without any increase in thrombo-embolic rate.[58] A reduction in haemorrhagic events (particularly gastrointestinal) was also noted, probably as a consequence of shorter duration of warfarin usage. This strategy now offers the opportunity to cardiovert AF of more than 48 hours duration without having to wait a month for anticoagulation with warfarin.

New drugs for atrial fibrillation

Dofetilide

Dofetilide is an anti-arrhythmic drug that has relatively pure class III properties. It exhibits reverse use dependence, with rate-related reductions in its capacity to prolong action potential duration and effective refractory period.[59] Dofetilide has a narrow therapeutic range and doses need to be adjusted on the basis of the renal function and effect on QT interval. In the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) study, 325 patients with AF or atrial flutter were randomised to 125, 250 or 500 µg of dofetilide twice-daily versus placebo.[60] The 500 µg dose achieved 30% cardioversion within 36 hours and 58% remained in sinus rhythm at one year. There were two cases of 'torsades de pointes' and one sudden cardiac death. It has a 28% efficacy in terminating AF and a 66% efficacy for atrial flutter when given intravenously, with a mean time to conversion of between 20–50 minutes.[61] 'Torsades de pointes' arrhythmias were reported in 4% of cases when dofetilide was given intravenously.

Ibutilide

Ibutilide is a pure class III agent approved in the United States for intravenous use in the acute termination of atrial flutter and fibrillation. Like dofetilide it is more effective at terminating atrial flutter (mean success rate 64%) than AF (33%) with an incidence of 'torsades de pointes' of 2.4%.[61] It also has effects on improving the success rate of cardioversion, primarily by lowering energy requirements for defibrillation by 30%.[32]

Azimilide

Azimilide is a class III anti-arrhythmic drug that has been shown to be more effective at terminating AF than dofetilide when given intravenously (success rate 93% versus 50%).[62] It may also have clinical effects in paroxysmal AF and flutter. In a dose-ranging trial of 384 patients with paroxysmal atrial arrhythmias, the drug was more effective than placebo at preventing AF recurrence.[63] It is extremely well tolerated with the incidence of adverse effects and mortality similar to placebo.[61]

Adenosine agonists

Adenosine is a naturally occurring substance that is used for a number of electrophysiological tests and treatments. The main limitations of adenosine are that it has an ultra-short half-life (10 seconds), has to be given intravenously and that it has significant vasodilator effects. The adenosine receptor agonist CVT-510 has been developed in an attempt to circumvent these problems. In a comparison study with diltiazem in guinea pigs, it slowed atrioventricular nodal conduction but without the negative inotropic, vasodilator and hypotensive effects seen with diltiazem.[64] There were no reported pro-arrhythmic effects. Should this drug reach clinical use there may be the potential for its use as a rate-controlling agent in AF without major adverse side effects.

Other drugs

Dronedarone is a non-iodinated derivative of amiodarone that has actions in all four of the Vaughan-William's classes. It is currently under development for oral and intravenous use in the treatment of AF.[65] Ambasilide, almokalant, sematilide and tedisamil are compounds with effects on the delayed rectifier potassium current that are also under clinical investigation for AF management.[66-69]

The future of anticoagulation therapy

Direct thrombin inhibitors are under development as a potential alternative to warfarin for the prevention of thrombo-embolic disease.[70] Ximelagatran, a prodrug of melagatran, is an orally active thrombin inhibitor under investigation for the prevention of stroke in AF.[71] It has a rapid onset of action and is administered on a weight-adjusted basis. Results from the SPORTIF III study are due to be published soon. This study showed a non-inferiority of ximelagatran compared with warfarin for the prevention of stroke (both ischaemic and haemorrhagic) and systemic thromboembolism (2.2% per year for warfarin and 1.3% per year for ximelagatran). The SPORTIF V data (randomising patients with AF to warfarin or ximelagatran) are eagerly awaited and are expected to be presented later this year.

Key messages

- Drug therapy for atrial fibrillation should be patient-tailored depending on aetiology and co-morbidity
- Both rate and rhythm control appear to be acceptable strategies for the elderly asymptomatic patient with persistent atrial fibrillation
- Most patients undergoing cardioversion should be pre-treated with an anti-arrhythmic drug to reduce the likelihood of early arrhythmia relapse

Conclusions

Drug therapy for the management of AF should be patient-tailored. In the asymptomatic elderly patient with AF, both rate control and rhythm control appear to be acceptable strategies providing that anticoagulation is continued. Digoxin has little effect at controlling the ventricular rate in active patients with permanent AF. Patients undergoing cardioversion of persistent AF should be pre-treated with anti-arrhythmic drugs (particularly amiodarone) to facilitate cardioversion and to improve the likelihood of maintaining sinus rhythm at one year. Direct thrombin inhibitors may offer an alternative to warfarin for the long-term anticoagulation of patients with AF.

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