Therapy for atrial fibrillation: new challenges

Eduard Shantsila, Timothy Watson & Gregory YH Lip†

†Author for correspondence
University Department of Medicine, City Hospital, Birmingham, B18 7QH, UK
Tel.: +44 121 554 3801
Fax: +44 121 554 4083
G.Y.H.LIP@bham.ac.uk

'Improvement in our understanding of pathophysiological mechanisms responsible for AF development also offers the challenge of revisiting pharmacological interventional targets of AF treatment.'

Atrial fibrillation (AF) represents the most common arrhythmia encountered in clinical practice, with its prevalence continuously increasing in the last few decades [1,2]. There is little doubt that AF poses a major public health problem, in view of the negative impact on quality of life, as well as the increased morbidity and mortality which relates to an increased incidence of stroke, thromboembolic events and heart failure [3,4].

Indeed, the loss of coordinated atrial contractions in AF creates a predisposition for thrombus formation within the atria and thereby contributes to the risk of embolic stroke in these patients. Whilst nonvalvular AF increases the risk of stroke approximately fivefold, valvular AF increases this risk up to 17-fold [5]. As many as 15% of all strokes in the USA may be attributable to AF [6]. AF is also associated with an increased number of emergency department visits and hospitalizations and frequent electrical cardioversions may be required despite the use of antiarrhythmic drugs.

In this situation, new therapeutic interventions for AF are constantly being sought. So, what are the challenges for this commonly encountered arrhythmia? The objectives of AF therapy are to reduce symptoms, prevent thromboembolic complications, and to eliminate detrimental effects on cardiac performance and longevity. Although the scientific knowledge regarding AF has significantly expanded, the management of AF patients is often problematic. Hence, guidelines for AF management are abundant. The consensus guidelines of the American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC) for the management of patients with AF published in 2001 [3] will be updated later in 2006, and the evidence-based UK NICE guidelines are now available [101]. A clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians is also available [7].

If AF is bad for us, perhaps sinus rhythm is better, being the more physiological and appropriate condition. Until recently, there was the clinical assumption that restoration and maintenance of sinus rhythm was the strategy of choice (a 'rhythm control' strategy), but because of insufficient efficacy of available antiarrhythmic agents it was difficult to achieve these objectives and AF tended to recur. For most antiarrhythmic drugs the recurrence rate is at least 50% during the first year post cardioversion [8,9]; however this figure may be somewhat lower with new agents, such as dofetilide [10], or old friends, such as amiodarone [11]. Recent randomized trials comparing a 'rhythm control' against a 'rate control' strategy have demonstrated that both have results in terms of mortality, although functional capacity may be improved by rhythm control [11,12]. Nonetheless, some patients with AF are symptomatic and may require restoration and maintenance of sinus rhythm. The cynic may argue that if we did have safe and highly efficacious pharmacological therapy, this may have obviated the need for these trials at their outset.

Improvement in our understanding of pathophysiological mechanisms responsible for AF development also offers the challenge of revisiting pharmacological interventional targets of AF treatment. Along with the dominant concept of AF as resulting from multiple reentrant circuits of various size and conduction velocities that propagate randomly through the atria [13] we increasingly recognize that electrical and structural remodeling promotes the perpetuation of AF. These changes include ionic current disturbances with a reduction in the L-type calcium ($I_{L_{Ca}}$) and transient outward potassium (Ito) currents, as well as atrial fibrosis and heterogeneous slowing of conduction related to activation of the renin–angiotensin–aldosterone system (RAAS), fibroblast proliferation, increased

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extracellular matrix protein deposition [14], inflammatory changes [15] and atrial dilatation. Recent demonstration of the presence of an ultra-rapid potassium current (I_{kur}) only in the atrium has opened the perspectives for new antiarrhythmic drug development, as the blockade of such ion currents would prolong repolarization only at the atrial level without any prolongation of ventricular repolarization, thus avoiding the risk of life-threatening arrhythmias.

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The critical role of the pulmonary veins (PVs) in AF pathogenesis has long been recognized. Although the precise mechanism by which the PVs contribute to AF-genesis remains unknown, the PVs may be a source of rapid repetitive activations that are independent of the left atrium, probably due to triggered activity and abnormal automaticity or reentry [16]. In addition, PV anatomy and atrial muscle fiber architecture surrounding the PVs are quite complex and varies between patients, with some changes in muscle fiber orientation [16]. This creates an anatomic substrate predisposing to anisotropic conduction and reentry. The demonstration of the effectiveness of focal PV ablation and PV isolation in some patients with AF underlines its important role in AF initiation and perpetuation [17]. However, the enthusiasm for PV isolation needs to be tempered by another recent study, where at the 6-month follow-up period, only 54% and 82% of patients remained free of arrhythmia-related symptoms after circumferential pulmonary vein ablation and after segmental pulmonary vein ablation, respectively [18]. In addition, asymptomatic episodes do frequently occur and may be significantly increased after catheter ablation, especially amongst previously symptomatic patients – thus, any follow-up strategy based on symptoms-only would substantially overestimate the success rate of ablation procedures [19].

Pharmacological cardioversion of AF is an appropriate option, being more effective in terminating recent onset compared with long-lasting AF, especially when initiated within 48 h after the onset of arrhythmia[3]. The Class IC antiarrhythmic agents (flecainide and propafenone) are effective and safe, both for AF termination and sinus rhythm maintenance in patients with normal hearts [20]In the presence of structural heart disease, the class III antiarrhythmics – ibutilide, dofetilide, amiodarone and sotalol – are drugs of choice [9] However, amiodarone – despite its side-effect profile – appears to be the most effective antiarrhythmic agent, especially in heart failure patients [9]. The pharmacological agents that are most commonly used to achieve heart rate control during AF include β-blockers, rate-limiting calcium-channel blockers and digoxin [21]

According to the current guidelines, it is necessary to consider anticoagulation for all patients with AF who have average or greater risk for stroke, unless there is a specific increased risk for bleeding, regardless of the type of arrhythmia (paroxysmal, persistent, permanent). However, taking into consideration the limited efficacy and significant risks of toxicity of available drugs, including potentially fatal adverse effects as well as deeper understanding of pathophysiological mechanisms give grounds for the efforts to find both more effective and safer drug therapies and alternative invasive technologies.

The new treatment technologies for AF management can be broadly divided into two categories: noninvasive and invasive. Investigational noninvasive treatment modalities are based on the development of new medications with antiarrhythmic and anticoagulant properties and new indications for existing drugs.

As the life-threatening complications of antiarrhythmic drugs are predominantly related to effects on ventricular electrophysiological modalities, the first group of new drugs exhibit atrial, selective antiarrhythmic properties. These drugs allow blockade of the atrial-specific, ultrarapid, delayed-rectifying potassium current (I_{Kur}) – such as AZD7009, AVE0118 or serotonin $(5\text{-HT})_4$ receptors. In preclinical studies, these drugs caused minimal ventricular pro-arrhythmias and were effective for rhythm control of AF. All of these drugs also combine blockade of other channels and can best be characterized as 'mixed-ion channel blockers'.

As class III antiarrhythmic agents were demonstrated to be effective in AF, the second group of new drugs are similar to amiodarone, and act by delaying repolarization by blocking outward potassium channels, but most importantly, blocking multiple-ion channels. The hope is that these drugs will retain the efficacy of amiodarone but will not be associated with its toxicity. This group includes such agents as dronedarone, azimilide and tedisamil.

Dronedarone is an investigational Phase III trial antiarrhithmic drug that is structurally similar to amiodarone but lacks the iodine group, which has been linked to many of its noncardiac side effects, including pulmonary toxicity, ocular effects, and thyroid and hepatic dysfunction. The Dronedarone Atrial FibrillatioN study after Electrical cardioversion (DAFNE) trial showed the efficacy of dronedarone in preventing AF recurrences after cardioversion in 199 patients [22]. The ANtiarrhythmic trial with DROnedarone in Moderate-to-severe congestive heart failure Evaluating morbidity DecreAse (ANDROMEDA) was stopped prematurely because of a potential trend showing an increased risk of death in the dronedarone group, but this increased mortality was not statistically significant. In the EURopean trial in AF or flutter patients receiving Dronedarone for the maintenance of sinus rhythm (EURIDIS) and its sister trial the American–Australian trial with DronedarONe In AF or flutter patients for the maintenance of Sinus rhythm (ADONIS), dronedarone had a benefit in prolonging the AF-free interval and also modestly decreased the ventricular response during AF recurrences. There was no evidence of proarrhythmia including no cases of torsades de pointes, heart failure exacerbations or thyroid/pulmonary/other organ toxicity, as well as a low mortality rate (1.0%) that was no.t different from placebo (0.7%) during the 12-month follow-up.

Several randomized, placebo-controlled clinical trials have also demonstrated efficacy of azimilide in prolonging the symptom-free interval in patients with AF or atrial flutter [23]. Azimilide has been proven safe and effective therapy for AF in patients with left ventricular systolic dysfunction after myocardial infarction. Azimilide also reduced the risk of asymptomatic AF recurrence by 40% compared with placebo [23] However, infrequent but serious adverse events include severe neutropenia and torsades de pointes, which occurred in up to 1.0 and 1.5%, respectively, of patients receiving the drug.

Tedisamil, being originally developed as an antianginal, was found to have significant class III antiarrhythmic properties and it has been shown to possess multiple-ion channel effects. Phase III studies in patients with ischemic heart disease indicated that tedisamil is an effective antianginal agent and its efficacy and safety in converting AF was recently assessed in a multicenter, double-blind, randomized, placebo-controlled study [24]. In studies, 41 and 51% of patients receiving the lower and higher doses, respectively, converted to sinus rhythm, with two cases (1.8%) of possible proarrhythmia (one episode of torsades de pointes and one of monomorphic ventricular tachycardia were observed).

RAAS blockade (with acetylcholinesterase inhibitors, angiotensin-receptor blockers or aldosterone blockers), steroids and statins which may prevent structural remodeling, fibrosis and inflammation represent 'old' drugs being increasingly used as 'new' treatments for AF and may be particularly useful in AF associated with congestive heart failure, hypertension or coronary artery disease or as adjunctive therapy in difficult-to-treat patients [25–27].

The interest in nonpharmacological therapies – particularly radiofrequency ablation for maintenance of sinus rhythm – has had a meaningful impact on rhythm-control strategies. Radiofrequency ablation is in evolution with different approaches in current use. The circumferential left atrium ablation strategy was found to be more effective than segmental ostial ablation, with a success rate at 6 months of 87 and 67%, respectively and unlike pulmonary venous isolation alone, may eliminate PV triggers [28]. Remote magnetic catheter navigation system for mapping and ablation of AF provides a new stage in interventional electrophysiology. However, the available data are insufficient to make reliable conclusions, especially since these strategies have not yet been evaluated in large properly designed randomized clinical trials with clinical end points.

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Affiliations

Eduard Shantsila, MD, Research Fellow
University Department of Medicine,
City Hospital, Birmingham B18 7QH,
UK

Timothy Watson, MRCP, Research Fellow
University Department of Medicine,
City Hospital, Birmingham B18 7QH,
UK

Gregory YH Lip, MD,
Professor of Cardiovascular Medicine
University Department of Medicine,
City Hospital, Birmingham B18 7QH,
UK
Tel.: +44 121 554 3801
Fax: +44 121 554 4083
G.Y.H.LIP@bham.ac.uk