Update on Atrial Fibrillation: Part II

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ABSTRACT

Antiarrhythmic drugs are an essential tool in the management of atrial fibrillation (AF). Although we are already on the threshold of a large expansion in the use of ablation therapies, these will not, however, be appropriate for all patients, and pharmacological therapies will continue to have an important place in the management of atrial fibrillation. The plethora of antiarrhythmic drugs currently available for the treatment of atrial fibrillation is a reflection that none is wholly satisfactory, each having limited efficacy combined with poor safety and tolerability. Improved class III antiarrhythmic drugs, such as dronedarone, new classes of antiarrhythmic agents, such as atrial repolarization delaying agents, and upstream therapies dealing with substrate, represent potential sources of new pharmacological therapies.

Key words: atrial fibrillation

Rate or Rhythm Control for Atrial Fibrillation

Recently published randomized studies comparing rate and rhythm control strategies have shown that primary rate control is not inferior to rhythm control, and furthermore, that rhythm control is more costly and inconvenient than is rate control.¹ This has led to a general movement away from rhythm control in patients who are able to tolerate the arrhythmia when the ventricular rate is adequately controlled. Primary rate control and anticoagulation are acceptable in elderly asymptomatic patients who probably constitute about 60%–70% of the atrial fibrillation (AF) population. However, in a large number of patients, there remains a genuine choice between rhythm and rate control. The primary rate control strategy is usually not appropriate in younger individuals, (i.e., less than 60–65 years) patients who are highly symptomatic, individuals with recent onset of AF, and patients with AF and associated congestive heart failure. Furthermore, the relationships between and within rate and rhythm control arms in the studies comparing the two strategies, and the reasons why rhythm control seems to be superseded by rate control, are far more complicated than has been outlined by the main reports. Analysis of subgroups showed that those who were in sinus rhythm and those who used anticoagulants survived better, while those who were treated with antiarrhythmic drugs had a higher mortality.² These results gave rise to speculation that the intuitive and demonstrable advantages of sinus rhythm could be offset by the toxicity of antiarrhythmic drugs and the failure to maintain adequate anticoagulation in those apparently restored to sinus rhythm. It is clear that antiarrhythmic drug therapy for rhythm control in AF patients is a complex treatment modality that requires careful patient selection, frequent monitoring for adverse

effects, and potentially frequent dosage or drug changes to achieve the best results. Currently available antiarrhythmic drugs like amiodarone, sotalol, dofetilide, propafenone, and flecainide, are moderately effective at initially reducing the incidence of paroxysms or preventing persistent AF, but patients may become unresponsive, develop tolerance, or side effects in the long-term.

New Antiarrhythmic Drugs

Ideally, an antiarrhythmic drug for AF would safely (without producing ventricular proarrhythmia) and effectively terminate and prevent recurrence of AF in patients with and without structural heart disease, would not exert negative inotropic effect or interfere with thromboembolic prophylaxis and would provide rate control (atrioventricular nodal blockade) during recurrence of AF. An attractive prospect for AF therapy is the introduction of agents with selective affinity to ion channels specifically involved in atrial repolarization, so-called atrial repolarization delaying agents (ARDAs). Other possibilities include modified structural analogues of traditional antiarrhythmic drugs with additional novel mechanisms of action and less complex metabolic profiles that may improve their efficacy and safety (e.g., slow release formulations of propafenone and flecainide, dronedarone, and modified amiodarone-based compounds) (Figure 1).

Atrial Repolarization Delaying Agents

The ultrarapid component of the delayed potassium rectifier current (I_{Kur}) is expressed in human atrial tissue but not in human ventricular myocardium. Thus, it is feasible to prolong atrial refractoriness without causing prolongation of the ventricular action potential and the QT interval and

increasing the risk of polymorphic ventricular tachycardia (torsade de pointes). Presently, there are several potential antiarrhythmic drugs with an ARDA mode of action which are currently in clinical development.³ Vernakalant (RSD 1235, Cardiome, Vancouver, Canada) is in the most advanced phase of development and investigation. The greatest efficacy (about 70%) was reported for recent onset of AF of less than 72 h in the Atrial arrhythmia Conversion Trial (ACT) I and III studies, which enrolled a total of 648 patients.⁴ However, the drug was ineffective for conversion of atrial flutter or AF of more than 7 days duration. An open-label ACT IV study will evaluate the safety of Vernakalant in 240 patients.

It is thought clinically useful to follow successful cardioversion of atrial fibrillation with the same or similar antiarrhythmic therapy for prevention of recurrences. An oral formulation of Vernakalant has now been evaluated in a phase II dose-ranging safety and efficacy study. The study demonstrated that 61% of patients treated with Vernakalant were in sinus rhythm 28 days after electrical cardioversion as compared with 43% of patients in the placebo group. There were no cases of drug-related torsades de pointes. A larger double-blind, placebo-controlled, randomized post-cardioversion study that will enroll approximately 670 patients is underway. Several potential antiarrhythmic drugs with an ARDA mode of action are currently in clinical development.

Dronedarone

Dronedarone (sanofi-aventis, Bridgewater, NJ, USA) is an investigational agent with multiple electrophysiological effects, in which it is similar to amiodarone, but it is devoid of iodine and is believed to have a better side-effect profile.⁵ The results of 2 efficacy and safety studies, EUROpean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS) and its American-Australian-African equivalent ADONIS, showed that dronedarone 400 mg twice daily was moderately superior to placebo in preventing recurrent AF, and was also effective in controlling ventricular rates. The post hoc analysis of these studies showed that patients treated with dronedarone had a 27% reduction in relative risk of death and hospitalization for cardiovascular causes. This observation is further explored in a phase III randomized study A placebo controlled, double blind Trial to assess the efficacy of dronedarone for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation and flutter (ATHENA) of approximately 4,000 high-risk patients which closed its recruitment in December 2006.

There is on-going research into the development of an amiodarone-derivative with modified binds within the

molecule allowing rapid hydalization, resulting in a more rapid action, a shorter half-life and possibly, a better risk-benefit ratio. Wyeth-Ayers, Madison, NJ, USA and ARYx have amiodarone-based agents with better safety profiles: aqueous amiodarone (Amio-Aqueous) and "soft" amiodarone (ATI-2042), respectively. Both compounds are in relatively early stages of development. The ATI-2042 is a rapidly metabolized chemical analogue of amiodarone with a half-life of 7 h, which is expected to have a similar efficacy profile to amiodarone but without the side effects attributable to long-term dosing and tissue accumulation. In a small phase 2a study, ATI-2042 reduced the amount of time that patients were in AF by 70%. The drug is under investigation in a phase IIb trial in paroxysmal AF.

Sanofi-aventis has a clutch of other amiodarone/drone-darone analogs at various stages of development. They have recently reported on celivarone (SSR149744C), a non-iodinated benzofurane derivative which exhibits multiple channel blocking properties and hemodynamic effects⁶ and is available in both intravenous and oral forms.

Azimilide and Tedisamil

Initial studies of azimilide, which blocks both I_{K_r} and I_{K_s} currents, were encouraging, but later post-cardioversion maintenance of sinus rhythm studies and all-comers maintenance programs showed less impressive results. Azimilide did not demonstrate clinically important or statistically significant efficacy in reducing the risk of arrhythmia recurrence and was associated with a high rate of torsades de pointes in patients with persistent AF.^{7,8}

Tedisamil produces multiple potassium channel blockade, including I_{K_r} , I , I_{KATP} , and a negative chronotropic effect by increasing gap junctional conductance and conduction velocity which may prevent fast ventricular rates during AF. Tedisamil has been abandoned as a long-term medication because of diarrhea due to blockade of the potassium current in the intestine and consequent hypokalemia and torsades de pointes, but is currently under investigation for acute pharmacological cardioversion of AF.

Innovative antiarrhythmic agents with unconventional antiarrhythmic mechanisms are now envisioned: stretch receptor antagonists, blockers of the sodium calcium exchanger, late sodium channel inhibitors, and gap junction modulators which may improve "the communication" between cells (Figure 1).¹

Upstream Therapies

There is accumulating evidence in support of the antiarrhythmic effects of traditional nonantiarrhythmic drugs (Table 1). Agents targeting inflammation, oxidative injury, atrial myocyte metabolism, extracellular matrix remodeling, and fibrosis, have theoretical advantages as potential

Figure 1: Currently available, investigational, and experimental antiarrhythmic agents for atrial fibrillation. ARDAs = atrial repolarization delaying agents; SAC = stretch-activated channels.

novel therapeutic strategies. Treatments with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), statins, and omega-3 polyunsaturated fatty acids (PUFAs) all seem promising, over and above any effect related to the treatment of underlying heart disease. A plethora of retrospective analyses from large randomized trials in myocardial infarction, congestive heart failure, and hypertension, the results from smaller prospective studies in AF, and 3 meta-analyses, have all suggested that therapy with ACEIs and ARBs may reduce risk of AF by approximately 20%–30%.^{9–11} The antiarrhythmic potential of these drugs will be addressed in several ongoing prospective trials in patients with AF.

Anti-inflammatory and antioxidant effects of statins can target specific mechanisms of AF. Statins may protect atrial myocytes during ischemia caused by rapid atrial rates through an increase in the synthesis of nitric oxide in the endothelium. Statins are employed in regulating a variety of matrix-degrading enzymes (matrix metalloproteinases) and thereby may attenuate extracellular matrix remodeling. In addition, simvastatin has been shown to reduce down-regulation of L-type calcium current, and therefore, prevent shortening of the atrial effective refractory period.¹² In a large registry of patients with left ventricular dysfunction, lipid-lowering drug use led to a sizeable 30% reduction in the incidence of new cases of AF independently of the lipid status.¹³ Pretreatment with atorvastatin for 1 week in 200 patients enrolled in the Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery (ARMYDA-3) trial reduced the incidence of in-hospital AF following an

open heart surgery from 57% in the placebo group to 35% (a 61% reduction in relative risk).¹⁴

It is thought that PUFAs can produce a membrane-stabilizing effect and may prevent stretch-induced shortening of atrial refractoriness, but evidence is unconvincing. Although 1 population-based study reported that greater intake of PUFAs consumed from fish (5 portions or more per week) was associated with a 31% reduction in risk of AF,¹⁵ others failed to reproduce these results.^{16,16a}

Nonpharmacological Treatment

Dissatisfaction with the current rhythm control drugs and discovering specific mechanisms of AF, such as very fast pulmonary vein tachycardia, led to the rapid development of nonpharmacological treatment alternatives, including various catheter-based percutaneous and surgical techniques.

Pulmonary Vein Isolation

Paroxysmal forms of AF can be treated with pulmonary vein isolation to prevent the induction of AF by rapid repetitive pulmonary vein ectopic activity emanating from “sleeves” of the atrial myocardium inside the pulmonary veins. In general, 2 different approaches have been adopted: anatomically based pulmonary vein isolation by circumferential ablation at their ostia, and segmental isolation of pulmonary veins guided by the detection of high-frequency depolarizations within the ostia (pulmonary vein potentials). Separate encirclement of both left-sided

TABLE 1: Upstream therapies for prevention of atrial fibrillation

Drugs	Mode of action	Evidence base
ACE inhibitors and ARBs	Targeting underlying heart disease (e.g., hypertension, heart failure) and unloading the atria Preventing structural remodeling: antifibrotic, antiapoptotic, and anti-inflammatory effects Anti-oxidant effects via PPAR-dependent pathways Direct electrophysiological effects on ion channels (e.g., inhibition of I_{Kur} , I_{to}) Preventing gap junctional remodeling Modulating the autonomic nervous system: antisympathetic activity Modulating thrombogenesis (e.g., antiplatelet effects, P-selectin inhibition)	Good experimental data Retrospective analyses Small prospective studies 3 meta-analyses Ongoing randomized controlled trials
Aldosterone antagonists	Unloading the atria in hypertension or heart failure Preventing structural remodeling: antifibrotic effects Direct electrophysiological effects on ion channels (e.g., inhibition of I_{Kur} , I_{to})	Sparse experimental data Clinical experience: prevention of sudden cardiac death; increased AF incidence in primary aldosteronism versus essential hypertension Small observational studies
Beta-blockers	Targeting underlying heart disease and unloading the atria Atrioventricular node blockade and rate lowering effect Membrane-stabilizing effect Modulating the autonomic nervous system: antiadrenergic activity	Retrospective analyses in heart failure and hypertension Clinical experience in CABG Small prospective studies Meta-analysis
Statins	Reducing cardiovascular events and the development of underlying heart disease Preventing substrate formation: anti-inflammatory and anti-oxidant effects Protecting the atrial myocardium during ischemia via increased e-NOS activity Preventing matrix remodeling via inhibition MMPs Preventing electrical remodeling by reducing downregulation of the I_{L-Ca} Modulating thrombogenesis (e.g., improved rheology, antiplatelet effects, fibrinogen reduction)	Experimental data Retrospective analyses and observational studies Prospective study in electrical cardioversion Prospective study in CABG Ongoing randomized controlled studies
Corticosteroids	Anti-inflammatory effects	Indirect evidence based on CRP reduction Small prospective studies Prospective studies in CABG and aortic valve surgery
n-3 PUFA	Preventing stretch-induced electrical remodeling Direct electrophysiological effects on ion channels (inhibition of I_{Na} , I_{L-Ca}) Reducing proarrhythmic eicosanoids in the myocardium Anti-inflammatory and anti-oxidant effects Preventing matrix remodeling via MMP-dependent mechanism	Experimental data Clinical experience: preventing ventricular fibrillation Analyses from the population-based studies Prospective study in CABG and after cardioversion Ongoing randomized controlled studies
PPAR antagonists (thiazolidinediones)	Anti-inflammatory, antiproliferative, and antioxidant effects Metabolic protection	Experimental data Case reports Retrospective analysis in postoperative AF (not yet completed)
pFox-inhibitors* (trimetazidine)	Altering atrial metabolism	No data

Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blockers; CABG = coronary artery bypass grafting; CRP = C reactive protein; eNOS = endothelial nitric oxide synthase; MMP = matrix metalloproteinase; PPAR = peroxisome proliferator-activated receptor; pFox = partial fatty acid oxidation; PUFA = polyunsaturated fatty acids. *Ramolazine is a potent inhibitor of the late sodium current and has therefore a direct antiarrhythmic effect, which significantly outweighs any potential protective effect on atrial metabolism

The eventual impact of pulmonary vein isolation is not yet known but it is likely to be successfully used in younger patients with paroxysmal AF and near-normal

New American College of Cardiology /American Heart Association/European Society of Cardiology (ACC/AHA-/ESC) guidelines have raised catheter ablation to the second choice in patients who failed at least one antiarrhythmic drug (Figure 2). However, the guideline committee emphasized that the long-term results of this strategy are not known and may not be as positive as the short- and medium-term outcomes suggest, whereas vital elements such as patient selection, optimum lesion sets, precise rates of freedom from AF without antiarrhythmic drugs, and the frequency of complications are incompletely defined. The necessity for continued anticoagulation after an apparently successful procedure has not been determined and the effect on mortality benefit is unknown. A large randomized trial Catheter Ablation versus Antiarrhythmic drug therapy for Atrial fibrillation (CABANA) will test whether left atrial catheter ablation will more effectively reduce total mortality than current rate control or antiarrhythmic drug therapy. Any patient with new onset of AF (over 65 years, or less than

TABLE 2: Randomized clinical trials of ablation therapies versus antiarrhythmic drug therapies for atrial fibrillation

Study	Number of patients	Type of AF	AF free at 1 year		Adjunct use of AAD in the ablation group
			Ablation	AAD/control	
Wazni et al, 2005 ¹⁷	70	96% paroxysmal	87%	37% (54% after the 2 nd AAD)	43% β -blockers
Stabile et al, 2005 ¹⁸ (CACAF)	137	67% paroxysmal	56%	9%; 57% crossed over to ablation	100% (by design)
Oral et al, 2006 ¹⁹	146	Persistent — cardioversion required	74%	4% (without amiodarone); 77% crossed over to ablation	100% amiodarone for 3 months, repeat ablation in 32%
Pappone et al, 2006 ²⁰ (APAF)	189	Paroxysmal	87%	29%; 51% crossed over to ablation	12%; repeat RFA in 4.6%
Jais et al, 2006* (A ⁴ study)	112	All paroxysmal	75%	7%; 63% crossed over to ablation	Not stated, but frequent repeat ablations (1.8 ablation procedures per patient)

* Presented at the 27th Annual Scientific Sessions of Heart Rhythm Society in Boston, Massachusetts. *Abbreviations:* AAD = antiarrhythmic drugs; AF = atrial fibrillation; APAF = Ablation for Paroxysmal Atrial Fibrillation study; CACAF = Catheter Ablation for the Cure of Atrial Fibrillation study; A⁴ = Atrial fibrillation Ablation versus AntiArrhythmic drugs)

or equal to 65 years of age, with other thromboembolic risk factors) who is suitable for participation in both strategies is eligible for the trial. Those randomized to the ablation limb will be further randomized to continue or discontinue anticoagulation.

Surgical Maze Procedure

The surgical maze procedure involves precise surgical incisions or lesions made with cryo- or radiofrequency-energy in the right and left atria, in order to interrupt the most common reentrant circuits responsible for AF.²⁴ Pulmonary veins are isolated and the left atrial appendage is excised, sutured or stapled. The surgical maze procedure is presently limited to patients undergoing other heart surgeries, (e.g., mitral valve repair or replacement [$<1\%$ of patients with AF]). In a recent meta-analysis of four randomized prospective trials and retrospective studies in patients with AF undergoing mitral valve surgery, a simultaneous maze procedure increased the likelihood of sinus rhythm by two-thirds and reduced the risk of stroke by 56% compared with mitral valve surgery alone.²⁵ As these operations become minimally invasive and highly effective they are likely to be more widely used.

Preventive Atrial Pacing

Although theoretically very attractive, preventive atrial pacing for the treatment of AF remains a debatable indication because limited data exist to provide sufficient evidence

for definitive management guidelines.²⁶ Atrial pacing can reduce the incidence of AF by modifying the substrate of the arrhythmia by capturing the areas with consistently prolonged activation times (e.g., coronary sinus ostium and Bachmann's bundle) or recognizing and suppressing potential triggers for AF using specific algorithms such as dynamic atrial overdrive pacing or anti-tachycardia pacing. Several ongoing studies will explore the role of preventive atrial pacing in selected patient populations as an additive to other therapies, such as cardiac resynchronization and antiarrhythmic drug therapy.

Conclusions

In summary, there are several new pharmacological agents recently released for the management of AF or currently under clinical investigation. New antiarrhythmic drugs targeting multiple channels, and having a high affinity to the atrial myocardium are believed to have more favorable risk/benefit ratio than traditional antiarrhythmic drugs. A broader perspective is being developed regarding the systemic, organ, tissue, myocyte membrane, and intracellular contributions to the genesis of AF. Catheter ablation therapy for AF has evolved rapidly, its widespread use fueled by several studies that have reported substantial advantage of catheter-based techniques over antiarrhythmic drugs when the rhythm control strategy is pursued. However, catheter ablation is not yet a well-proven therapeutic option for broader AF populations, and its long-term effects and

impact on all-cause mortality are unknown. Furthermore, even if new drugs, devices, or catheter-based approaches do prove superior to current therapies, their benefits must be very substantial (retaining high efficacy with added safety and convenience) in order to offset their inevitably greatly increased cost. Preventive therapies with agents targeting specific AF mechanisms such as, angiotensin II mediated remodeling, inflammation, oxidative injury, atrial myocyte metabolism, extracellular matrix remodeling, and fibrosis, have theoretical advantages as potential novel therapeutic strategies.

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