New antiarrhythmic agents for atrial fibrillation

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Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, with an incidence that increases twofold every decade after 55 years of age. Despite recent advances in our understanding of the mechanisms of AF, effective treatment remains difficult in many patients. Pharmacotherapy remains the mainstay of treatment and includes ventricular rate control as well as restoration and maintenance of sinus rhythm. In the light of studies demonstrating safety concerns with class IC agents, class III agents such as sotalol and amiodarone have become the preferred and most commonly used drugs. Unfortunately, a plethora of side effects often limits the long-term use of amiodarone. Thus, there have been many recent developments in antiarrhythmic drug therapy for AF that have gained more interest, particularly with the recent debate over rate versus rhythm control. It is hoped that the availability of the newer agents will at least provide a greater choice of therapies and improve our management of this common arrhythmia.

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Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice [1]. It affects 5% of the population above the age of 65 years and 10% above 75 years [2]. AF accounts for 35% of USA hospitalizations for cardiac arrhythmias [3]. Its presence increases mortality twofold, mostly through stroke and heart failure. In view of the aging population, AF is likely to be an even greater public health problem.

There have been many recent developments in antiarrhythmic drug therapy for AF which have gained more interest, particularly with the recent debate over rate versus rhythm control for AF [4]. Although restoration of sinus rhythm has traditionally been the main focus of AF management, recently published trials have compared the strategy of rate control versus rhythm control as the primary aim in the treatment of AF and suggested that neither may be superior, in relation to long-term symptoms, quality of life, mortality and morbidity [4].

These trials do have some limitations, but based on the combined evidence from the randomized controlled trials, future management for the majority of AF patients is likely to be centered on rate control and anticoagulation rather than cardioversion, and much of the treatment needs to be individualized [4]. However, rhythm control should still be considered in 'lone' AF and in those patients who are very symptomatic, as well as remaining the target of treatment in paroxysmal AF. New antiarrhythmic agents therefore still have some role, especially since many existing ones have significant side effects and limitations of efficacy.

Pathophysiology of AF: a brief overview

The genesis of AF is not entirely clear [5]. Similar to most cardiac arrhythmias, the basic mechanisms can be discussed under three categories.

Disorder of impulse generation

Enhanced automaticity of atrial myocytes around the pulmonary veins can act as initial triggers for episodes of paroxysmal AF [6]. Radiofrequency ablation of this focus can therefore result in a 'cure' of AF [7]. Indeed, ablation has been very successful in the selected group of patients where there has been drug intolerance or ineffectiveness and many such patients have demonstrated improvement in symptoms and quality of life following such treatment.

Disorder of impulse conduction

During sinus rhythm, the impulse generated from the sino-atrial node is unidirectional in conduction because of the refractoriness of the preceding myocardium. However, if this impulse encounters an area of refractory myocardium, its progression as a wavefront is broken. Following its circuit around this area, the wavefront may return to its point of origin after the refractory period has finished and re-excite the myocardium, thereby setting up a re-entry circuit. In chronic AF, multiple re-entrant waves wander over the atria supported by areas of functional

conduction block. These waves collide and divide and maintain the chaotic electrical state of chronic AF.

Combined mechanisms

These include both enhanced automaticity and abnormal conduction. The role of the autonomic function has also been postulated and forms of AF that are predominantly vagotonic or adrenergic have been described. In the clinical setting this has been less useful, since many patients often have features of both.

The remodeling phenomenon

The success rate of cardioversion is higher when AF is of short duration and the likelihood of recurrence postcardioversion decreases after a few weeks [9–11]. These findings suggest that AF is a progressive and self-perpetuating disease, which maintains itself via a phenomenon described as electrical and structural remodeling.

The hallmark of electrical remodeling is the shortening of the atrial effective refractory period (AERP) associated with loss of the rate dependency of the AERP. These alterations which appear within minutes to hours of the onset of AF, increase atrial vulnerability and are self-perpetuating. The classic demonstration of this was by Wijffels and coworkers in a goat model of AF, who demonstrated that after pacing-induced AF, the initial AF episodes self-terminated but on repeated stimulation, the episodes became longer in duration until sustained AF was established – referred to as 'AF begets AF' [12].

It is thought that within minutes of rapid atrial rate, there is intracellular calcium overload, which decreases the trans-sarcolemmal calcium gradient and hence reduces calcium-induced activation of the L-type channel, with consequent reduction in L-type calcium current, I_{Cal}. This phenomenon, termed 'pseudo-remodeling', shortens the refractory period [13]. In cases of persistent atrial tachycardia of longer duration (hours to days), there is downregulation of the L-type calcium and sarcoplasmic reticular (Ca^{2+})-ATPase gene [14]; indeed, this is probably the basis of true electrophysiological remodeling. When this rapid atrial rate persists even longer (weeks to months) structural changes take place (hibernation, fibrosis and fatty degeneration), which can be irreversible [15–17].

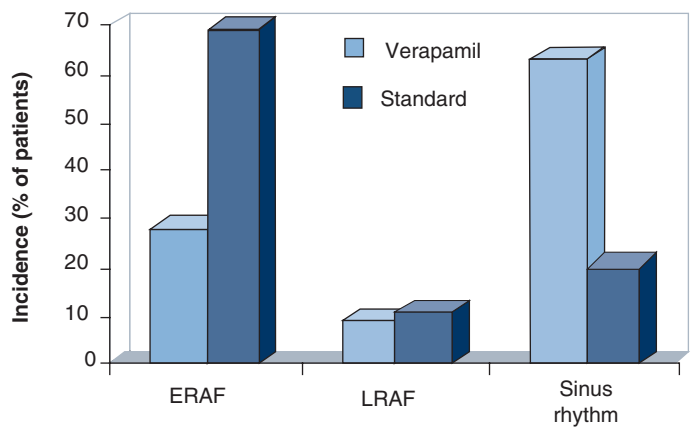
Preventing atrial remodeling with drugs

Prevention of AF recurrence in patients with paroxysmal AF, or the long-term maintenance of sinus rhythm after successful cardioversion is difficult, with most recurrences occurring within the first 5 days [11]. The increased vulnerability to recurrence is most likely secondary to AF-induced atrial electrophysiological remodeling, as described above.

The above hypothesis was supported by animal experiments which suggested infusion of verapamil significantly reduced electrical remodeling [18], whilst digoxin (which promotes calcium overload) may aggravate this phenomenon [19]. Certainly, there is growing clinical evidence even in humans that pretreatment with verapamil could reduce the early recurrence of AF after successful cardioversion [11,20,21]. This also seems to be applicable for other calcium antagonists, including diltiazem and dihydropyridines [11]. At the same time, the lack of benefit from long-term treatment with verapamil strongly supports the hypothesis that recovery from electrical remodeling occurs in a few days and after this period, these drugs may only play a marginal role in preventing recurrence [20,21] (**Figure 1**).

Recent studies suggest AF in the setting of congestive cardiac failure may be mediated through mechanisms that differ from those reported in the atrial-tachycardia-induced models [22]. Indeed, atrial dilation and fibrosis seem to play a major

Table 1. Data from the VERAF study [21].



The effect of administration of standalone verapamil (240 mg/day) from 1 month before to 1 month after electrical cardioversion (CV) of persistent AF as compared with standard therapy (in which no antiarrhythmic agents were used) on ERAF, LRAF and consequent maintenance of sinus rhythm 1 month after CV. Verapamil was significantly more effective in preventing ERAF ($p < 0.001$) but had no beneficial effect on LRAF.
AF: Atrial fibrillation; ERAF: Early recurrence of AF (7 days);
LRAF: Late recurrence of AF (8–30 days)

role in this setting and the observed changes in AERP are opposite to that seen in the tachycardia model, that is an increased AERP [22]. These changes may be prevented by treatment with the angiotensin-converting enzyme (ACE) inhibitors [23] or angiotensin II receptor blockers – the beneficial effects of these groups of drugs have also been noted in the atrial tachycardia model [24]. For example, the results of the first prospective and randomized trial conducted in humans [25] showed that adding the angiotensin II receptor antagonist, irbesartan, to amiodarone was more effective in maintaining sinus rhythm after successful cardioversion of AF, when compared with amiodarone alone. In this study, irbesartan reduced both the immediate (1 h) and subacute recurrence (first few weeks) of AF.

The mechanisms underlying the beneficial effects of renin–angiotensin system blockade (with the ACE inhibitors and angiotensin II receptor blockers) remain speculative but may be related to one of the following mechanisms:

- Decreased atrial stretch
- Reduction of left ventricular end-diastolic pressure
- Prevention and regression of atrial fibrosis
- Modulation of autonomic balance
- Prevention of ion current alterations with subsequent reversal of atrial remodeling
- Reduction of blood pressure

Further randomized prospective trials are needed to establish the actual role of verapamil and renin–angiotensin blockade (and their combination) in preventing recurrence of AF, as well as the possible synergistic effect in combination with antiarrhythmic drugs.

Classification of AF & current management approaches

Various terminologies are used to describe different subtypes of AF – acute, paroxysmal, recurrent, persistent and permanent. The term chronic AF is often loosely used to encompass all the subtypes of AF, other than acute AF. Lack of uniformity of these terms often results in difficulties in comparing studies on AF, effectiveness of treatments or therapeutic strategies.

'Acute AF' usually occurs in context of a precipitating illness, such as myocardial infarction, thyrotoxicosis, chest infection, or secondary to positive chronotrophic agents as often seen in the critical care setting. It is important for the clinician to ascertain whether an incident of AF is the very first episode i.e., the initial event and whether it is symptomatic or not, self-terminating or not, in order to formulate a long-term management plan. Treatment of the underlying cause is usually sufficient to restore sinus rhythm but if the AF causes hemodynamic compromise then electrical cardioversion may be required, or rate control may be needed in the acute setting using β-blockers, rate-limiting calcium channel blockers (although it should be noted that some of these are also negative ionotropes) or amiodarone. Class I agents are usually avoided because of the risk of provoking serious ventricular arrhythmias or acute heart failure. Digoxin, although positively ionotropic and rate-limiting, is not the best

Table 1. Antiarrhythmic drugs to restore sinus rhythm in atrial fibrillation.

Drug	Route	Time to efficacy	Efficacy (%)	Side effects (%)
Propafenone	Intravenous	<4 h	43–89	0–17
	Oral	<5 h	72–86	10–14
Disopyramide	Intravenous	<8 h	55–86	7
Quinidine	Oral	<24 h	59–92	3–46
Flecainide	Intravenous	<2 h	65–96	7–31
	Oral	<5 h	78–95	21–23
Amiodarone	Intravenous	<12 h	25–89	7–27
Sotalol	Intravenous	<4 h	31–85	10–20
Ibutilide	Intravenous	<90 min	18–48	4
Dofetilide	iIntravenous	<2 h	30–35	3–8
	Oral	<36 h	6–18	

Different classes of antiarrhythmic agents appear to yield similar results. However, certain factors must be taken into account if one is to compare and evaluate the real differences between these drugs, namely, the route of administration, the 'time to efficacy', incidence of adverse events, the duration of AF, underlying clinical condition, left ventricular function, the presence or absence of any organic heart disease and finally the placebo effect (which is consistently around 50% at 12–24 h in durations of AF of 48 h or less).

drug to use in acute AF because of its slow onset of action and its reduced rate-limiting effect in the presence of sympathetic overdrive. It should also be noted that digoxin use may be associated with increased mortality in the setting of acute myocardial infarction [26].

Episodes of paroxysmal AF usually self-terminate within 48 h and, by definition, in fewer than 7 days. If the patient has had two or more episodes, AF is said to be recurrent. The aim of management in this group of patients is reduction in frequency and duration of paroxysms of AF and maintenance of sinus rhythm. Class IC drugs (flecainide [Tambocor®, 3M Pharmaceuticals, MN, USA], propafenone [Rythmol®, Abbott Laboratories, CA, USA]) administered orally or intravenously represent the first-choice therapy in patients with no organic heart disease [27–30]. However, in the presence of heart failure, ischemic heart disease or after coronary artery bypass surgery, this group of drugs is associated with increased mortality [31] and amiodarone is the preferred drug (**Table 1**).

When an episode of AF has lasted longer than 7 days, it is designated as 'persistent'. The timeframe of 7 days, although arbitrary, represents the limit beyond which spontaneous cardioversion is unlikely to occur. Electrical cardioversion (preferably with a biphasic defibrillator) currently plays a major role [32]. However, maintenance of sinus rhythm can be difficult with a recurrence rate of 50–60% at 6–12 months [33–36]. Concurrent treatment with antiarrhythmic agents may increase the success rate (**Table 2**). However, given the evidence from the recent rate versus rhythm trials, future management of the majority of these patients is likely to be centered on rate control and anticoagulation, rather than an aggressive cardioversion policy for all patients with AF.

Table 2. Maintaining sinus rhythm after electrical cardioversion.

Drug	Sinus rhythm (%)	
	6 months	12 months
Propafenone	40	–
Disopyramide	44-50	54
Quinidine	27–58	23–51
Flecainide	–	34–42
Amiodarone	75	50–73
Sotalol	44–50	37–46
Dofetilide	71	66

Established or permanent AF refers to those patients in whom AF has been present for a long time and in whom cardioversion has not been indicated, or one or more attempts have failed to restore sinus rhythm. Established AF or permanent AF may be the first presentation of a non-self-terminating arrhythmia or be preceded by recurrent self-terminating episodes. In these patients, the main aim is rate control and antithrombotic therapy. This is generally achieved with class IV agents (diltiazem, verapamil), class II agents (β–blockers) or digoxin. Amiodarone may have a role to play, particularly in patients with AF and congestive cardiac failure. Monotherapy is often found to be inadequate in 24 h and exercise-induced heart rate control, whereas combination therapy (e.g., digoxin plus β-blocker or rate-limiting calcium antagonist [37]) should be considered as it may be useful not only in achieving satisfactory ventricular rate but also in reducing the dosage of individual drugs and, consequently, dose-dependent side effects.

In summary, the goals of management in AF should be tailored both to the patient and the type of AF. Careful definition of the subtype of AF and patient characteristics help define management goals and the right antiarrhythmic drug choice. Despite recent advances in our understanding of the pathophysiology of AF, effective treatment still remains difficult in many patients. In view of the limited role of nonpharmacological agents, drug therapy remains the mainstay of treatment. The limitations in current treatments leave the door open for the development of new antiarrhythmics with improved efficacy, safety and favorable side-effect profile.

New antiarrhythmic agents

The main emphasis in research and development has been on agents that would be used for cardioversion or maintenance of sinus rhythm. Thus, class I and III agents that prolong the refractory period and thus prevent re-entry have been researched the most. Their mechanism of action and development can be discussed according to whether they are class I or III agents, combination agents, modification of existing agents or *de novo* agents (**Table 3**).

Drugs with class IC action

The current role of IC agents has been largely limited to patients with paroxysmal AF and to facilitate electrical cardioversion in persistent AF, provided there is no history of ischemic heart disease

Table 3. Mechanism of action of new antiarrhythmic drugs.

Class	Antiarrhythmic agent	Mechanism of action	Route of adminstration
I	Pilsicainide Dofetilide	Pure Na channel blocker Blocks I_{kr}	Oral Oral/Intravenous
III	Ibutilide Azilimide Tedisamil	Blocks I_{kr}, stimulates INa Blocks I_{kr}, I_{Ks} Blocks I_{kr}, I_{KTo}, I_K ATP	Intravenous Oral Intravenous
Multichannel blocker	Ersentilide Dronedarone SD3212	Blocks I_{Kr} and b1 Blocks I_{Na}, I_{Ca}, IL, I_{Kr}, I_{Ks} and I_{K1} Blocks I_{Na}, I_K, I_{Ca}	Intravenous and oral Oral Intravenous
Novel antiarrhythmics	Piboserod (SB207266) RSD1235 CVT-2759, CVT-510, SHA-040	5HT4 antagonist, blocks I_{kr} Blocks atrial potassium (Kv1.5) and sodium channel Partial agonist to A1- adenosine receptor	Oral Intravenous and oral Intravenous

or heart failure. Thus, the current aim is to develop pure class IC agents without a significant negative inotropic action.

One such agent is pilsicainide (Sunrythm®, Suntory Limited), which has been shown to block sodium channels without any significant action on Ca^{2+} or K^+ channels [38]. In patients with recent onset AF, a single oral dose of pilsicainide (150 mg) achieved cardioversion to sinus rhythm in 45% of patients within 90 min, compared with 8.6% in the placebo arm [39]. In the setting of chronic AF (average duration of 22 months) treatment with 150 mg once daily of oral pilsicainide for 4 weeks achieved pharmacological cardioversion in 21%. Of the remaining, 69% were successfully cardioverted electrically after 4 weeks of pretreatment. Pilsicainide was also found to be reasonably successful in maintaining sinus rhythm in this subgroup of patients (34% after 2 years) [40]. Potential side effects include AV dissociation and QTc prolongation, especially in association with dehydration or renal disease, as the drug is actively secreted by the proximal convoluted tubule.

Drugs with class III action

The terminal phase of repolarization of an action potential is mediated by outward delayed rectifier K^+ currents, I_k. This can be separated pharmacologically into two components: a rapidly acting component I_{kr} and a slower component I_{ks}.

Dofetilide (Tikosyn®, Pfizer), ibutilide (Corvert®, Pharmacia & Upjohn), tedisamil® (Solvay pharmaceuticals), E4031, D-sotalol and almokalant are I_k-blockers and thus produce only prolongation of action potential duration (and hence of QT interval). Initial trials using dofetilide and ibutilide have shown promising results in their role in attaining and maintaining sinus rhythm.

Dofetilide is a pure class III agent that selectively blocks I_{kr} and has been licensed in the USA for maintenance of sinus rhythm. Its pharmacological profile includes a linear dose–plasma concentration relationship and also a linear plasma concentration–QTc effect. The blockade by dofetilide of I_{kr} increases with hypokalemia causing a disproportionate increase in the duration of action potential and the QTc. Thus, the correction of hypokalemia and hypomagnesaemia is of crucial importance in preventing and treating QT prolongation and torsade de pointes (3–4%). Conversely, hyperkalemia blunts its effect [41], suggesting the possibility of reduced efficacy after acute coronary occlusion or during rapid heart rates, when local cardiac tissue hyperkalemia may occur. It also exhibits reverse use-dependence, that is, its effects decrease with increasing heart rate. This results from the rate induced enhancement of other repolarizing ionic currents (principally I_{ks}) and the accumulation of K^+ in the intracellular clefts.

Dofetilide has been shown to be moderately effective in cardioverting persistent AF (both orally and intravenously) and significantly effective in maintaining sinus rhythm after pharmacological and electrical cardioversion. Data from the European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide (EMERALD) [42] and the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) [43] trials demonstrated a conversion

to sinus rhythm of 30% of patients with long-lasting AF with a dose of 500 µg orally twice daily for 3 days. Oral dofetilide also appears to be significantly effective in maintaining sinus rhythm, with 71 and 60% of the patients remaining in sinus rhythm after 6 months and 1 year respectively. In the EMERALD trial, dofetilide achieved significantly higher conversion as well as maintenance of sinus rhythm, when compared with sotalol (Betapace®, Bristol Myers Squibb). Even in patients with symptomatic heart failure and left ventricular dysfunction dofetilide was found to be significantly better than placebo at maintaining sinus rhythm ($p < 0.0001$) and reducing risk of hospitalization from heart failure [44]. Although no mortality difference was observed between the two groups, treatment was initiated with 3 days of intensive cardiac monitoring and dose-adjustment and most cases of torsade de pointes occurred during this period. A number of potential interactions with commonly used drugs have also been described – verapamil (increases oral absorption), cimetidine (inhibits renal excretion), ketoconazole (Nizoral®, Janssen Cilag, reduces hepatic excretion), diuretics (by causing hypokalemia). Thus, the safety of initiating dofetilide in the community is questionable. Dose adjustment according to the length of the QTc interval and creatinine clearance (when GFR < 60ml/min) along with correction of hypokalemia reduces the risk of this potentially life-threatening arrhythmia.

On the other hand, studies with ibutilide (Corvert®, Pharmacia & Upjohn) have focused in its ability to achieve cardioversion – which appears greater than dofetilide (Tikosyn®, Pfizer) – rather than maintenance of sinus rhythm, as the drug is available only in an intravenous form [45,46], in view of its high first-pass metabolism. This drug has been licensed in the USA for the acute termination of both atrial fibrillation and atrial flutter but is unavailable in the UK. Ibutilide is predominantly an I_{kr}-blocker, thereby prolonging atrial and ventricular refractoriness and action potential duration, but also activates a slow inward sodium current. In view of the relatively high incidence of torsade de pointes (3–4%) it should be used with caution in a monitored setting. QT prolongation is dose-dependent, maximal at the end of the infusion and return to baseline within 2–4 h following infusion (elimination half-life 3–6 h). The incidence of torsade de pointes can be further reduced by strict maintenance of potassium and magnesium levels within normal limits.

Ibutilide is also effective as an adjunct to direct current (DC) cardioversion, when pretreatment with 1mg ibutilide was associated with a 100% success rate, as opposed to 72% with DC cardioversion alone [47]. Interestingly, all patients who initially failed DC cardioversion were subsequently successfully cardioverted with ibutilide and DC cardioversion. Ibutilide was also found to significantly reduce the mean energy requirement for cardioversion from 228–166 J. Even in patients who were chronically on amiodarone, the addition of 2 mg of ibutilide intravenously resulted in cardioversion of 54% of the patients with atrial flutter and 36% of those with AF [48]. Of the remaining, 90% had successful electrical cardioversion. This suggests that combination therapy may be a useful method for achieving cardioversion for patients with chronic AF, particularly in adjunction with direct current cardioversion (DCC) and in those with negative response to monotherapy. However, given the current trend towards rate control and anticoagulation in persistent and chronic AF and the fact that alternative drugs are available to terminate recent onset AF, the risks and benefits of ibutilide administration should be carefully considered for each patient to minimize pro-arrhythmic adverse events.

The option of safe but effective arrhythmic drugs in the setting of coronary artery disease and left ventricular dysfunction is pretty limited. Tedisamil, another class III agent is undergoing development with a potential to occupy this niche. As an effect of its multi-channel-blocking properties (**Table 3**), tedisamil produces bradycardia, prolongs the action potential in both the atria and ventricle and increases the ventricular refractory period [49]. Another major advantage is the lack of negative inotropic action. Though tedisamil has been shown to be effective in a dose-dependent fashion in increasing angina threshold and reducing the frequency of angina, it also exhibits reverse dose-dependence, thus limiting its efficacy with exercise and rendering β-blockers superior [50]. In animal studies, tedisamil has been shown to be effective in preventing and reversing ventricular arrhythmia in the ischemic setting [51]. In a recently concluded Phase II trial in patients with symptomatic AF or atrial flutter, tedisamil dose-dependently converted patients to sinus rhythm [52]. There was also a dose-dependent increase in QT, a slight increase in blood pressure and a decrease in heart rate.

The dual antiarrhythmic and anti-ischemic properties of tedisamil, without negative inotropism, make it an attractive novel agent for use in AF with coexisting ischemia. Concerns over a coexisting increase in vascular resistance mean that further evaluation is required in patients with left ventricular dysfunction to avoid the risk of decompensation of heart failure. Furthermore, the development of oral formulation and evaluation of the optimal dosage is essential for continuing therapy in the community.

One of the major limiting factors of I_{kr}-blockers has been reverse dose-dependence, due to offsetting of I_{kr} and enhancement of other ionic currents, principally I_{ks}. This led to the development of azimilide, another class III agent which was designed to specifically block Iks, however there is evidence to suggest that it also blocks I_{kr} [53]. In the canine model, azimilide has been shown to be superior to dofetilide in terminating acute AF and unlike the latter, its effects on effective refractory period (ERP) were rate-independent [54]. In patients with paroxysmal atrial fibrillation (PAF), azimilide has been found to significantly lengthen the arrhythmia free interval compared with placebo [55]. Subgroup analysis reveal increased efficacy in patients with ischemic heart disease and congestive heart failure. The azimilide postinfarct survival evaluation (ALIVE) study demonstrated that azimilide had neither beneficial nor adverse effects on reducing all-cause mortality in patients who had had a recent myocardial infarction [56]. Twice the number of patients in the placebo group developed AF compared with the treatment group but the numbers were small (19 and 8 respectively). The safety of azilimide in high-risk patients has been further demonstrated by Singer and colleagues [57] who found that azimilide decreases recurrent ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators (hazard ratio = 0.31, $p = 0.0001$). Furthermore, its excellent oral absorption, long half-life of 110 h, lack of need for dose alteration in renal and hepatic dysfunction and the absence of any major drug interaction makes azimilide an interesting proposition. Adverse effects are in the form of a small risk of torsade de pointes and rarely, neutropenia.

Another nonselective class III agent, ambasilide, has shown similar effects to sotalol in experimental studies on dogs but no conclusive clinical studies have been evaluated in humans.

Drugs with more than one class action

I_{kr} blockade is ineffective in preventing ventricular fibrillation elicited by the interaction between acute myocardial ischemia and elevated sympathetic activity. This depends in part on the fact that sympathetic activity offsets more than 50% of the action potential prolonging effect of I_{kr} blockade.

Ersentilide, which has a combined action I_{kr} and weak β-adrenergic blockade, represents an effective and safe option to overcome this problem. In one canine study, ersentilide seems to prevent ventricular fibrillation in the post myocardial infarction setting [58]. Further work is ongoing, regarding its potential role in AF and ischemic heart disease patients. Success of combination therapy in some trials have lead to further research in an effort to develop drugs with multiple class actions. One such drug is SD3212, with class I, III and IV actions and in a rabbit model appeared to raise the threshold of AF by its combined actions [59].

Modification of existing drugs

The long-term use of amiodarone, probably the most effective antiarrhythmic available, is largely limited by its wide spectrum of side effects, some of which are due to its iodine base. Dronedarone, a benzofurane derivative without iodine substituents shares similar electrophysiological properties with amiodarone [60] (**Table 3**). A recent Phase II study has suggested 800 mg once daily as the safe and effective dose for preventing AF relapses following cardioversion [61]. There was no evidence of thyroid, ocular or pulmonary toxicity during the 6 month follow-up period. Nonetheless, further studies are needed to further delineate the antiarrhythmic and safety profile of this drug.

Novel antiarrhythmics

Serotonin receptor antagonists

Serotonin (5HT) is known to exert positive chronotropic and inotropic effects on the human atria [62]. Hence, it has been postulated that serotonin can induce supraventricular arrhythmias [63] and thus the blockade of the 5HT4 receptors expressed on the atria would suppress these arrhythmias. Accordingly a 5HT4 receptor antagonist, SB207266 (piboserod), has been developed as a potential new treatment for AF and is currently undergoing Phase II trials.

Atrial selective antiarrhythmic agents

Due to the nonselective action of currently available drugs on both the atria and ventricle, significant adverse effects in the form of myocardial

depression and torsade de pointes are often encountered. RSD-1235 is a novel, mixed ion channel antagonist that selectively blocks the atrial potassium (Kv1.5) and sodium channels in a dose-dependent fashion, thus prolonging the atrial refractory period without significantly affecting the ventricular refractory period [64–66]. A recently completed Phase II trial showed high dose RSD-1235 significantly terminated recent onset AF within 30 min of dosing (61% conversion compared with 5% for placebo) [67]. In addition, 10 of the 11 patients remained in sinus rhythm after 24 h. The availability of an oral preparation, rapid onset of action (75% oral bioavailability within 15–30 min) and relatively short half-life of 2 h, makes it an attractive agent for use in the acute termination of AF with the potential for being used in prehospital settings. The currently ongoing Phase III trials would further clarify the safety and efficacy of this drug.

Adenosine receptor agonists

Adenosine produces acute inhibition of sinus node and AV nodal function. This profound but short lived electrophysiologic effect is exerted via adenosine A1 receptors [68] which are maximally concentrated around the AV node with some representation in the atria and minimal expression on the ventricular myocardium. This receptor distribution explains the lack of negative inotropic effect of adenosine.

Potent 'complete' agonists of A1 receptors are limited by their causation of high-grade AV block, profound bradycardia, atrial fibrillation (shortens atrial effective refractory period) and vasodilation (adenosine 2A receptors) [69]. However, experiments on guinea-pig heart have shown CVT-2759 (a partial agonist of A1 receptors) to selectively prolong cardiac AV nodal conduction time while causing minimal sinus bradycardia, shortening of the duration of the atrial monophasic action potential, or coronary vasodilation. At concentrations above 10 µmol its action on the AV node reaches a plateau thus reducing the risk of heart block but at these concentrations it causes mild coronary vasodilation [68] which is most likely to be beneficial in patients with a background of IHD. Another A1 partial agonist, CVT-510, has been found to slow AV nodal conduction at least equivalent to diltiazem, but without causing the negative inotropic, vasodilatory and hypotensive effects associated with diltiazem [70].

In summary, partial agonists of A1 receptors have the therapeutic potential for treating supraventricular tachycardias (SVTs) that incorporate the sinus node or AV node as part of the arrhythmia circuit, unmasking atrial tachyarrhythmias or ventricular pre-excitation and for ventricular rate control in permanent AF.

HIghlights

- Despite recent advances in our understanding of the pathophysiology of atrial fibrillation, effective treatment remains difficult in many patients.
- Currently available drugs are reasonably effective in converting paroxysmal atrial fibrillation into sinus rhythm and in enhancing the electrical effects of cardioversion.
- The current choice of antiarrhythmic drugs is limited in patients with structural heart disease, ischemic heart disease and left ventricular dysfunction.
- These limitations in current treatments leaves the door open for newer antiarrhythmic agents with improved efficacy, safety and side effect profile.

Outlook & conclusions

Despite recent advances in our understanding of the mechanisms of AF, effective treatment remains difficult in many patients. Pharmacotherapy remains the mainstay of treatment and includes control of ventricular rate as well as restoration and maintenance of sinus rhythm.

Of the new antiarrhythmics, ibutilide seems to have the most to offer for cardioversion to sinus rhythm, especially as adjunct to DC cardioversion in the setting of recent-onset AF and as part of combination therapy in chronic AF. However, as the drug is administered intravenously and the risk of pro-arrhythmia is greatest shortly after administration, it should be used in a closely monitored setting. The new class I agent, pilsicainide may prove as effective as ibutilide in achieving cardioversion but some concern will still remain about using this group of drugs in patients known or suspected to have ischemic heart disease. On the other hand, dofetilide shows some promise as an agent for maintaining sinus rhythm, although in view of the frequency of QTc prolongation and torsade de pointes early in the treatment, its initiation in the community might be problematic. Despite limited clinical data, both azimilide and dronedarone seem to have the potential to play a role in the long-term maintenance of sinus rhythm in patients with AF.

Thus, the potential of new antiarrhythmic drugs to improve our management of AF and atrial flutter poses exciting new possibilities. However, their uptake in clinical practice will depend not only on their efficacy as antiarrhythmic agents but also on their safety in acutely terminating AF and in long-term maintenance of sinus rhythm in the community.

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