LEADING ARTICLE

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Novel Approaches for Pharmacological Management of Atrial Fibrillation

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Abstract

In the light of the progressively increasing prevalence of atrial fibrillation (AF), medical awareness of the need to develop improved therapeutic approaches for the arrhythmia has also risen over the last decade. AF reduces quality of life and is associated with increased morbidity and mortality. Despite several setbacks as a result of negative results from rhythm control trials, the potential advantages of sinus-rhythm (SR) maintenance have motivated continued efforts to design novel pharmacological options aiming to terminate AF and prevent its recurrence, with a hope that optimized medical therapy will improve outcomes in AF patients.

Pathophysiologically, AF is associated with electrical and structural changes in the atria, which increase the propensity to arrhythmia perpetuation but may eventually allow for new modalities for therapeutic intervention.

Antiarrhythmic drug therapy has traditionally targeted ionic currents that modulate excitability and/or repolarization of cardiac myocytes. Despite efficacious suppression of ventricular and supraventricular arrhythmias, traditional antiarrhythmic drugs present problematic risks of proarrhythmia, potentially leading to excess mortality in the case of Na^+-channel blockers or I_{Kr} (I_{Kr} = the rapid component of the delayed rectifier potassium current) blockers. New anti-AF agents in development do not fit well into the classical Singh and Vaughan-Williams formulation, and are broadly divided into 'atrial-selective compounds' and 'multiple-channel blockers'.

The prototypic multiple-channel blocker amiodarone is the most efficient presently available compound for SR maintenance, but the drug has extracardiac adverse effects and complex pharmacokinetics that limit widespread application. The other available drugs are not nearly as efficient for SR maintenance and have a greater risk of proarrhythmia than amiodarone.

Two new antiarrhythmic drugs are on the cusp of introduction into clinical practice. Vernakalant affects several atrially expressed ion channels and has rapid unbinding Na^+-channel blocking action along with promising efficacy for AF conversion to SR. Dronedarone is an amiodarone derivative with an electrophysiological profile similar to its predecessor but lacking most amiodarone-associated adverse effects. Furthermore, dronedarone has shown benefits for important clinical endpoints, including cardiovascular

mortality in specific AF populations, the first AF-suppressing drug to do so in prospective randomized clinical trials.

Agents that modulate non-ionic current targets (termed 'upstream' therapies) may help to modify the substrate for AF maintenance. Among these, drugs such as angiotensin II type 1 (AT_1) receptor antagonists, immunosuppressive agents or HMG-CoA reductase inhibitors (statins) deserve mention. Finally, drugs that block atrial-selective ion-channel targets such as the ultra-rapid delayed rectifier current (I_{Kur}) and the acetylcholine-regulated K^+-current (I_{KACh}) are presently in development.

The introduction of novel antiarrhythmic agents for the management of AF may eventually improve patient outcomes. The potential value of a variety of other novel therapeutic options is currently under active investigation.

The incidence and prevalence of atrial fibrillation (AF) are continuously rising. Epidemiological projections have forecast a >2-fold increase in AF prevalence among the North American population, to over 12 million affected patients by the year 2050, and this projection would only hold if there was no additional rise in incidence. If the incidence were to rise, as it did between 1980 and 2000, we will experience an even more pronounced increase in AF prevalence (projected to almost 16 million affected individuals).[1]

Clinically, AF is importantly associated with cardiovascular diseases such as systemic arterial hypertension and heart failure.[2,3] With improved treatment options for acute cardiovascular conditions (such as improved interventional therapies for acute myocardial infarction [MI]) and better long-term therapies for severe cardiac diseases, such as congestive heart failure (CHF) and valvular heart disease, more patients will survive to a chronic phase and a greater number of patients will be affected by complicating disorders such as AF.

1. Pharmacological Approaches to Atrial Fibrillation (AF) Therapy

1.1 Underlying Arrhythmia Mechanisms

AF typically occurs in the setting of specific structural and electrophysiological changes in the atria that contribute to perpetuation of the arrhythmia. These alterations are termed 'atrial remodelling'.[4] Atrial remodelling can involve primarily changes in the function and distribution of cardiac ion channels (electrical remodelling) or primarily changes in atrial tissue architecture, particularly interstitial fibrosis and atrial dilatation (structural remodelling). Structural and electrical remodelling can, of course, also co-exist. While remodelling provides a substrate necessary to maintain AF, triggers that initiate the arrhythmia may arise from ectopic activity within the pulmonary veins[5] or relate to Ca^{2+} handling abnormalities associated with the arrhythmia[6] or with underlying AF-promoting conditions such as CHF.[7]

In addition to remodelling related to underlying cardiac conditions, AF itself causes changes that play a significant role in AF pathophysiology.[8] Rapid atrial activation, as occurs with AF, leads to progressive shortening of atrial action potential duration (APD) due to downregulation of L-type calcium current ($I_{Ca,L}$)[9,10] and increases in inward-rectifier K^+ currents such as the background current (I_{K1}) and the constitutively activated acetylcholine-regulated current ($I_{KACh,c}$).[11] Shortened APD allows for smaller re-entry circuits and acceleration/stabilization of re-entrant rotors, helping to perpetuate the arrhythmia,[12] as reflected by increases in dominant frequency of atrial rotors with longstanding AF.[13] Rotors are spiral waves with an excitable but unexcited core that can act as generators for re-entrant arrhythmia maintenance (for discussion, see Jalife et al.[14] and Comtois et al.[15]). In addition, regional heterogeneities in atrial

refractoriness and abnormalities in atrial conduction are important for AF maintenance.[16,17] For a detailed review of changes in ionic currents and structural elements, we refer the interested reader to an article by Nattel et al.[4]

Because of rate-dependent remodelling caused by any form of rapid atrial tachyarrhythmia, multiple wavelet re-entry may represent a final common pathway for persistent AF caused by various pathological conditions.[9] According to the leading circle hypothesis, maintenance of re-entry depends on the 'wavelength', or distance travelled by an impulse during its own effective refractory period (ERP). Mathematically, wavelength is expressed by the product of conduction velocity and ERP.[18] The greater the atrial wavelength, the fewer re-entrant circuits can be accommodated in the atria and the more likely it is that all re-entry circuits terminate simultaneously. Accordingly, shortening of APD (and consequently ERP) and/or decrease of conduction velocity will decrease the wavelength, increase the number of potential re-entry circuits, and lead to increased vulnerability and sustainability of AF.[9] Both APD and conduction velocity can be modulated by antiarrhythmic drug therapy.

1.2 Principles of Antiarrhythmic Drug Action

Traditionally, antiarrhythmic drugs are classified into groups according to the Singh and Vaughan-Williams classification.[19,20] Drugs of Singh and Vaughan-Williams class I are Na^+-channel blockers that were originally subspecified according to effects on APD and ERP. As these drugs decrease conduction velocity, their application should promote re-entrant arrhythmia according to classical leading circle theory.[21,22] Their paradoxical benefit for AF, primarily a re-entrant arrhythmia, was an enigma for many years. Recent work has shown that class I antiarrhythmic drugs increase the excitable gap (difference between AF cycle length and atrial ERP) during AF, along with the central diameter of AF-maintaining rotors, leading to extinction of the rotors.[23,24] Experimental data in animal models and mathematical modelling work have pointed to three mechanisms leading to extinction of rotors and AF termination.[25] First, the centre of rotors enlarges with decreased fast sodium inward current (I_{Na}) availability. The enlarged rotors show increased meander and greater likelihood to extinguish at anatomical or functional boundaries. Finally, there is a reduction in the number of daughter rotors that could maintain the arrhythmia upon extinction of primary arrhythmia-maintaining generators. In addition, class I drugs suppress ectopic foci from pulmonary veins,[26,27] contributing to arrhythmia termination.[28] In line with these findings, clinical use of class I antiarrhythmic compounds (flecainide, propafenone) for conversion of short-lasting AF (<48 hours) is well established and highly effective.[29,30] The lack of class I antiarrhythmic drug efficacy in longstanding AF relates to progressive remodelling, possibly involving structural changes, in the later stages of AF.[31]

APD is the single most important determinant of ERP, and APD prolongation is the central mechanism of antiarrhythmic action for Singh and Vaughan-Williams class III compounds.[32] ERP prolongation increases the wavelength, potentially terminating AF and preventing its re-induction. CHF reduces the slow component of the delayed rectifier current component (I_{Ks}), with repolarization depending more importantly on the rapid component (I_{Kr}).[33] Pharmacological inhibition of this current with dofetilide (a pure class III agent) significantly increases ERP,[34] prominently increasing wavelength and effectively terminating AF in experimental CHF models. Dofetilide has also effectively been applied to patients with heart failure.[35] Efficacy of class III compounds for cardioversion of AF in other settings is limited as a result of prominent reverse-use dependence, producing greater efficacy at slower activation rates and less ERP prolongation at the rapid rates of AF.[36]

1.3 Traditional Antiarrhythmic Drug Therapy: Usefulness and Limitations

Traditional pharmacological approaches to AF treatment primarily involved antiarrhythmic agents that were originally developed to treat ventricular arrhythmias. Not surprisingly, these

agents have prominent effects on the ventricles, with electrophysiological action that can lead to proarrhythmia. Both class I and III drugs can suppress AF, but have limitations related to limited efficacy and to risks of adverse effects. Presently, class I agents are primarily used in patients without significant structural heart disease, while class III drugs are used when the risk of drug-induced excess APD (QT interval) prolongation and ventricular proarrhythmia are low. Sotalol and amiodarone are effective agents with class III properties and success in sinus rhythm maintenance ranges between ~50–80% after 1 year.[37] The efficacy of pharmacological treatment depends on the duration of AF prior to initiation of therapy.

Results of CAST (for a list of trial acronyms, see table I) indicated detrimental effects of Na^+-channel blockers (i.e. encainide and flecainide) on survival in patients with ventricular arrhythmias post-MI.[38] A meta-analysis of data in AF patients treated with quinidine suggested similar detrimental effects.[39] The class III agent dexsotalol (D-sotalol), which targets I_{Kr} selectively, also caused excess post-MI arrhythmic mortality.[40] Most class III agents are associated with risks of ventricular proarrhythmia due to drug-induced long-QT syndromes.[41]

More recent evidence regarding presently available antiarrhythmic drugs emerged from the rate versus rhythm control trial AFFIRM.[42] *Post hoc* analyses indicated that sinus rhythm was either a determinant or marker of improved survival but that currently available antiarrhythmic drugs did not enhance survival, suggesting that beneficial effects of sinus rhythm maintenance may be offset by untoward effects of drug treatment.[43]

Table I. Trial acronyms and full names

Acronym	Full name
ACTIVE	Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events
ADONIS	American-Australian-African trial with DronedarONe In atrial fibrillation/flutter patients for the maintenance of Sinus rhythm
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
ANDROMEDA	ANtiarrhythmic trial with DROnedarone in Moderate to severe congestive heart failure Evaluating morbidity DecreAse
ANTIPAF	Angiotensin II Receptor Blocker in Paroxysmal Atrial Fibrillation trial
ATHENA	A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization of death from any cause in patiENts with Atrial fibrillation/flutter
CAST	Cardiac Arrhythmia Suppression Trial
CTAF	Canadian Trial of Atrial Fibrillation
DAFNE	Dronedarone Atrial FibrillatioN study after Electrical cardioversion
DIONYSOS	Efficacy and safety of Dronedarone versus amiOdarone for the maintenance of sinus rhYthm in patientS with atrial fibrillation
ERATO	Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRondArone for the cOntrol of ventricular rate during atrial fibrillation
EURIDIS	EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm
GISSI-AF	Gruppo Italiano per lo Studio della Streptochinasi nell''Infarto miocardio - Atrial Fibrillation
LIFE	Losartan Intervention For Endpoint reduction in hypertension

bid = twice daily.

2. New Drugs for AF Therapy

Novel agents developed to treat AF do not fit too well into the classical Singh and Vaughan-Williams classification and are broadly separated into categories such as 'atrial-selective compounds' like vernakalant (albeit still affecting multiple ionic currents, see section 2.1), 'multi-channel blockers' such as dronedarone (see section 2.2) or fall into the category of 'upstream therapies' including statins, inhibitors of the renin-angiotensin system and immunomodulatory agents (section 2.3).[44] The first two parts of this section summarize basic and clinical pharmacological data for two novel antiarrhythmic compounds that are in advanced phases of pharmaceutical development and clinical evaluation. While vernakalant is an antiarrhythmic agent with predominantly 'atrial-selective' action, dronedarone is a prototype of the 'multi-channel blockers'. Section 2.3 discusses the novel concept of 'upstream' therapies.

2.1 Vernakalant

Vernakalant ((1R,2R)-2-[(3R)-hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride) is an antiarrhythmic compound with predominant actions on atrial electrophysiology. It was developed as an atrial-selective compound in order to circumvent the shortcomings, particularly ventricular proarrhythmia, of traditional antiarrhythmic compounds (figure 1).[45]

2.1.1 Pharmacokinetic Profile

Vernakalant (previously RSD1235) is metabolized by the cytochrome P450 (CYP) 2D6 isoenzyme into less active metabolites that are excreted as glucuronide conjugates. Pharmacogenetic analyses have recently been published for intravenously administered vernakalant in several clinical trials.[46] In healthy volunteers, plasma concentrations of vernakalant increased with increased administration (0.1–5.0 mg/kg) and decreased exponentially after the end of infusion. Maximum concentrations (C_{max}) were obtained at the end of 10-minute infusions and the plasma elimination half-life was slightly longer within higher dosage groups (mean ~2 hours). The pharmacokinetics of vernakalant were linear over the dose range evaluated and C_{max} increased proportionally with the dose. Vernakalant had a volume of distribution of ~2 L/kg, indicating significant tissue binding. Among this population of healthy volunteers, total body clearance of vernakalant ranged from 649 to 938 mL/min.

2.1.2 Pharmacodynamic Effects

Vernakalant affects cardiac Na^+ channels and several K^+ channels that are predominantly expressed in the atria (table II).[45] Vernakalant blocks Kv1.5 channels (corresponding to native ultra-rapid delayed rectifier current) predominantly in the open state, with preserved efficacy at increased stimulation rates.[47] Its effects on Na^+ channels are voltage- and frequency-dependent, leading to enhanced inhibitory potency with depolarized potentials and more rapid frequencies. In particular, vernakalant exhibits rapid unbinding from Na^+ channels, a property that has recently been identified as a promising characteristic for drugs used to treat AF.[48] These properties provide atrial-selective actions based on rapid atrial activation during AF and relatively depolarized membrane potentials compared with ventricular cells.[47] Vernakalant terminates and prevents induced early afterdepolarizations (EADs, the mechanism underlying long-QT syndrome arrhythmias[4]) in rabbit Purkinje fibres.[49] In the same study, the authors documented a protective effect of vernakalant against methoxamine/clofilium-induced Torsade de pointes (TdP) in a rabbit model. The effects on EADs and TdP were attributed to inhibition of late Na^+ current.

Table II. Acute ion channel blocking properties of vernakalant *in vitro*

Target	Effect (IC_{50})	Species/cell type/conditions	Reference
$I_{NaV1.5}$	~9 μmol/L	Heterologous expression in HEK cells, recording at RT	47
I_{to}	~15 μmol/L	Rat ventricular myocytes, recording at RT	47
I_{HERG}	~21 μmol/L	Heterologous expression in HEK cells, recording at RT	47
$I_{Kv1.5}$	~13 μmol/L	Heterologous expression in HEK cells, recording at RT	47
I_{K1}	>1 mmol/L	Guinea-pig ventricular myocytes, recording at RT	47
$I_{Ca,L}$	~22 μmol/L	Guinea-pig ventricular myocytes, recording at RT	47
I_{KACh}	10 μmol/L	Rat atrial myocytes	45

HEK = human embryonic kidney; **HERG** = human ether-a-go-go related gene; **IC_{50}** = concentration of half maximal inhibitory effect; **$I_{Ca,L}$** = L-type Ca^{2+} current; **I_{HERG}** = HERG current – corresponding to native rapid delayed rectifier K^+ current; **I_{K1}** = background inward rectifier K^+ current; **I_{KACh}** = acetylcholine-regulated K^+ current; **$I_{Kv1.5}$** = Kv1.5 current – corresponding to native ultra-rapid delayed rectifier K^+ current; **$I_{NaV1.5}$** = SCN5A current – corresponding to native I_{Na}; **I_{to}** = transient outward K^+ current; **RT** = room temperature.

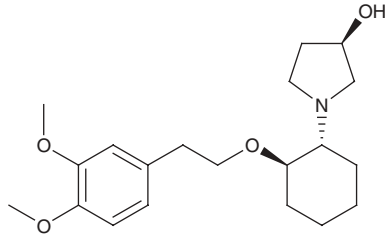


Fig. 1. Chemical structure of vernakalant (molecular weight = 386).

2.1.3 Effects on ECG Parameters in Patients

In vivo human electrophysiology studies indicate atrial selectivity with significantly greater prolongation of atrial versus ventricular refractory periods.[50] While infusion of vernakalant 4 mg/kg over 10 minutes followed by 1 mg/kg/hour for 35 minutes slightly prolonged atrioventricular conduction time (by ~5%; $p < 0.05$) and sinus node recovery time (by ~13%; $p < 0.05$); however, it did not affect the QT interval. There have also been only minor changes in QT interval in treatment studies in AF. The first study published reported a nonsignificant ~3% increase in QT interval[51] and the second publication reported an increase in corrected QT (QTc) [Bazett] by ~5% ($p < 0.001$),[52] possibly related to I_{Kr} inhibition.

2.1.4 Clinical Trials of Vernakalant in AF

Intravenous vernakalant rapidly and effectively terminated recent-onset AF in a dose-finding study.[51] In this study, 56 patients with AF of 3–72 hours duration were randomized to one of two vernakalant dose groups or to placebo. The vernakalant groups received either 0.5 mg/kg of the agent followed by 1 mg/kg or 2 mg/kg followed by 3 mg/kg via intravenous infusion over 10 minutes. Patients treated with the higher dose of vernakalant had a greater rate of AF termination compared with placebo (61% vs 5%, $p < 0.0005$). There were more patients in sinus rhythm at 30 minutes (56% vs 5%; $p < 0.001$) and at 1 hour (53% vs 5%; $p = 0.0014$) and median time to AF conversion was shorter (14 vs 162 minutes; $p = 0.016$). There were no serious adverse events related to vernakalant administration, indicating safety as well as efficacy of drug treatment.

In a phase III clinical trial, patients with short- (3–7 days, $n = 220$) or long-lasting (8–45 days, $n = 116$) AF were randomized to receive either vernakalant 3 mg/kg or placebo.[52] In the short-duration group, 51.7% of patients converted rapidly to sinus rhythm compared with only 4.0% of patients receiving placebo ($p < 0.001$). Median time to conversion with vernakalant was 11 minutes. Vernakalant was ineffective for conversion of longstanding AF and effects were not statistically different from placebo (conversion rate 7.9% vs 0%; $p = 0.09$). Dysgeusia and sneezing were noted in ~30% and ~16% of vernakalant-treated patients, respectively. There were no incidences of TdP arrhythmia within the 24-hour period following cardioversion despite mild but statistically significant QT interval prolongation. One episode of TdP was observed 32 hours after drug administration. Other vernakalant-related serious adverse events occurred in four patients (hypotension in two, complete atrioventricular block and cardiogenic shock occurred). Another phase III efficacy study indicated safe and efficient AF conversion with vernakalant among patients with post-operative AF.[53] Phase I studies of an oral formulation, modified to obviate a short plasma half-life by providing sustained absorption, have also been completed, but results have not been published as a full article.[54]

2.1.5 Relative Clinical Efficacy of Vernakalant

There is no evidence from direct comparative studies regarding the AF conversion efficacy of vernakalant. A comparative study evaluating differences between amiodarone (5 mg/kg over 1 hour, then maintenance of 50 mg for another hour) and vernakalant (3 mg/kg over 10 minutes followed by 2 mg/kg if the patients is still in AF after 15 minutes observation) is currently ongoing. Recruitment for the trial is expected to conclude at the end of May 2009 after a scheduled enrolment of 240 patients with AF of 3–48 hours duration. Based on the data provided by Roy et al.,[52] ~50% of patients are expected to convert to sinus rhythm within 1 hour after vernakalant administration. Data from a trial performed in the 1980s indicated superiority of intravenous amiodarone (5 mg/kg) over verapamil for conversion of recent onset AF. In this study, amiodarone was effective in ~70% of patients after a follow-up of 3 hours.[55] Results from the direct comparison are awaited with great interest.

2.2 Dronedarone

Dronedarone (*N*-(2-butyl-3-{4-[3- (dibutylamino)propoxy]- benzoylbenzofuran-5-yl) methansulfonamid) was synthesized based on the

amiodarone molecule. Structural modifications were introduced to avoid the toxicity risks of amiodarone.[56] Modifications included the removal of the iodine molecules, with the goal of eliminating iodine-related organ toxicity (particularly on the thyroid gland), and the addition of a methane-sulphonyl group to decrease lipophilicity, thereby reducing tissue accumulation (figure 2).

2.2.1 Pharmacokinetic Profile

The elimination half-life of dronedarone in humans is approximately 24 hours, much shorter than the half-life for amiodarone, which can be many days. Dronedarone bioavailability is only ~15% because of extensive first-past hepatic metabolism (CYP3A4 isoenzyme) making twice-daily administration necessary to obtain adequate steady-state plasma concentrations. In a dose-finding study, a 2-fold increase in dronedarone dose led to a 2.65- and 2.40-fold increase in dronedarone and *N*-debutyl metabolite concentrations, respectively. The mean metabolic ratio (*N*-debutyl metabolite/dronedarone) was ~0.6 for any given dose.[57]

Interactions between dronedarone and metoprolol (a CYP2D6-metabolized agent) have been noted in a randomized pharmacokinetic study that enrolled 49 healthy CYP2D6 genotyped male subjects.[58] During a period of 13 days, the addition of dronedarone (800–1600 mg/day) to metoprolol (200 mg/day) increased the bioavailability of metoprolol in CYP2D6 extensive metabolizers and induced an additive dronedarone dose-dependent negative inotropic effect. Nevertheless, at 800 mg/day (the currently used therapeutic dose) these effects were modest.

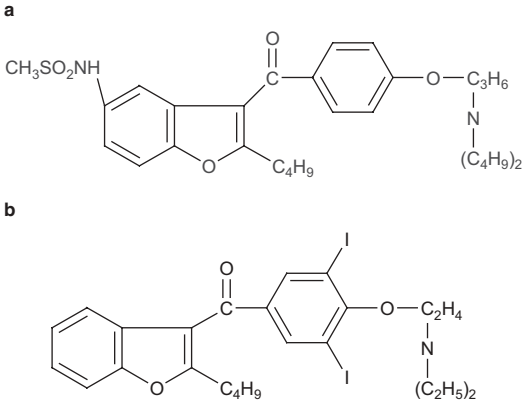


Fig. 2. Chemical structure of (**a**) dronedarone (molecular weight = 593) and (**b**) amiodarone (molecular weight = 682).

2.2.2 Pharmacodynamic Effects

Dronedarone functions as a blocker of multiple ion channels and exhibits non-competitive anti-adrenergic activity.[56,59,60] The inhibitory effects of short-term dronedarone administration are summarized in tables III and IV. The compound reversibly inhibits a set of K^+ currents, $I_{Ca,L}$, sodium-calcium exchanger and Na^+ current. The lack of APD prolongation with short-term dronedarone administration in animal models may relate to this balanced influence on depolarizing and repolarizing currents. There is heterogeneity among various cardiac regions (left vs right ventricle or Purkinje fibres) in response to the drug. Dronedarone leads to no change or even a shortening of APD in most regions (left ventricular [LV] transmural APD or Purkinje cells), but may slightly increase right ventricular APD (table IV[64]).

2.2.3 Comparison with Long-Term Amiodarone Administration

Given the well known differences in effects between short- and long-term administration of amiodarone,[70] several investigations have evaluated the effect of long-term oral administration of dronedarone compared with the predecessor compound.

Dronedarone may be even more effective than amiodarone at influencing parameters of ventricular repolarization. In rabbit atrial muscle, long-term (4 weeks) oral dronedarone 100 mg/kg/day led to a prolongation of action potential duration to 90% repolarization (APD_{90}) by ~19%, while short-term dronedarone administration shortened APD_{90} (table IV). This effect was qualitatively similar to that observed with amiodarone (100 mg/kg/day) in the same model.[67] The same authors had previously evaluated effects on ventricular APD_{90} in a similar model (5-week oral administration). In this study, dronedarone 100 mg/kg/day produced

Table III. Acute ion channel blocking properties of dronedarone *in vitro*

Target	Effect	Species/cell type/conditions	Reference
I_{KACh}	IC_{50}: 63 nmol/L	Rabbit sinus node cells recorded at RT ACh 10 μmol/L to activate I_{KACh}	61
I_{KACh}	IC_{50}: ~10 nmol/L	Guinea-pig atrial cells recording temp. not provided CCh 10 μmol/L to activate I_{KACh}	62
I_{HERG}	IC_{50}: ~9 μmol/L	Expressed in *Xenopus* oocytes recorded at RT	63
$I_{KvLQT1/minK}$	50% tail current reduction with 100 μmol/L	Expressed in *Xenopus* oocytes recorded at RT	63
I_{Kr}	IC_{50}: <3 μmol/L	Guinea-pig ventricular myocytes recorded at 35 ± 1°C	59
I_{Kr}	~97% reduction with 10 μmol/L	Canine ventricular myocytes recorded at 37°C	64
I_{Ks}	IC_{50}: ~10 μmol/L	Guinea-pig ventricular myocytes recorded at 35 ± 1°C	59
I_{K1}	IC_{50}: >30 μmol/L	Guinea-pig ventricular myocytes recorded at 35 ± 1°C	59
$I_{Ca,L}$	IC_{50}: ~180 nmol/L	Guinea-pig ventricular myocytes recorded at 35 ± 1°C	59
$I_{Ca,L}$	~77% reduction with 10 μmol/L dronedarone	Canine ventricular myocytes recorded at 37°C	64
I_{Na}	~97% reduction with 3 μmol/L	Human atrial myocytes recorded at RT	65
I_{NCX}	IC_{50}: inward NCX 33 μmol/L IC_{50}: outward NCX 28 μmol/L	Guinea-pig ventricular myocytes recorded at 35 ± 1°C	66

Ach = acetylcholine; **CCh** = carbachol; **HERG** = human ether-a-go-go related gene; **IC_{50}** = concentration of half maximal inhibitory effect; **$I_{Ca,L}$** = L-type Ca^{2+} current; **I_{HERG}** = HERG current – corresponding to native rapid delayed retifier K^+ current; **I_{K1}** = background inward rectifier K^+ current; **I_{KACh}** = acetylcholine-regulated K^+ current; **I_{Kr}** = rapid component of the delayed rectifier K^+ current; **I_{Ks}** = slow component of the delayed rectifier K^+ current; **$I_{KvLQT1/mink}$** = corresponding to native I_{Ks} current; **I_{Na}** = Na^+ current; **I_{NCX}** = Na^+/Ca^{2+} exchange current; **NCX** = Na^+/Ca^{2+} exchange; **RT** = room temperature; **temp** = temperature.

greater prolongation of APD_{90} (27% vs 15%; $p < 0.05$) at a cycle length of 300 ms compared with amiodarone. This prolongation of ventricular APD also translated into a prolongation of the QT interval of conscious rabbits (~30% increase from 140 ± 9 to 183 ± 9 ms for dronedarone 100 mg/kg/day).[71]

Results obtained in a canine model of chronic atrioventricular block showed a small but significant increase in QTc interval with long-term oral dronedarone for 3 weeks (20 mg/kg twice daily). In this same study, shortening of ventricular APD_{90} with short-term administration of dronedarone (table IV) suppressed almokalant-induced TdP. Intravenous dronedarone (2.5 mg/kg/10 minutes) abolished ventricular ectopic activity and polymorphic ventricular tachycardia through shortening of QT interval and normalization of T-U wave morphology.[69] In contrast, a study in healthy dogs fed 25 mg/kg (twice daily) dronedarone for 4 weeks demonstrated absence of QTc interval prolongation, whereas amiodarone (50 mg/kg once daily) led to significant QTc interval prolongation.[64] Consistently, canine papillary muscle APD_{90} was not prolonged with long-term dronedarone administration. There was a small but significant use-dependent reduction of phase 0 upstroke velocity (V_{max}) with dronedarone, while amiodarone exhibited strong V_{max} reductions.

Differences in thyroid hormone-dependent gene expression between amiodarone and dronedarone have been noted in rat hearts.[72] Thyroid receptor ($TR_{\alpha 1}$) expression was similarly reduced by amiodarone and dronedarone in the right atrium (potentially contributing to heart rate reduction), whereas expression of $TR_{\alpha 1}$ was increased with amiodarone but not dronedarone in the LV apex. Experimental animals subjected to rapid atrial pacing showed $I_{Ca,L}$ α_{1c}-subunit downregulation due to electrical remodelling, a change that is prevented by amiodarone, possibly contributing to the efficacy of the compound.[73] It is presently unknown whether dronedarone exerts similar effects.

2.2.4 Effects on ECG Parameters in Patients

Dronedarone dose-dependently prolonged PR interval by 13.4, 16.6 and 28.4 ms in 800, 1200 and 1600 mg/day groups, respectively, with QTc

intervals prolonged by 39 ms in the highest dosage group (1600 mg) compared with placebo (figure 3; $p < 0.0024$).[57]

In two clinical efficacy trials for AF treatment (see section 2.2.5), effects of dronedarone on mean heart rate, QT and QTc intervals were pre-specified analyses. Compared with placebo, dronedarone significantly affected all three parameters: heart rate reduction was ~7%, while QT and QTc were prolonged by ~23 and ~9 ms respectively, ($p < 0.001$ for all comparisons).[74] Despite this QT interval prolongation, ventricular arrhythmias occurred infrequently in both treatment arms and no episodes of TdP were observed.

2.2.5 Clinical Trials of Dronedarone in AF

Several prospective, randomized, double-blind, multicentre clinical trials of dronedarone have been completed (table V). The first study published was the DAFNE trial, indicating safety and effectiveness of dronedarone at a dosage of 400 mg twice daily.[57] This study was designed as a dose-finding study and evaluated dronedarone 800, 1200 and 1600 mg/day for AF relapse prevention in 270 patients with persistent AF. It appeared puzzling that no clear dose-response pattern emerged. This finding could not be explained by pharmacokinetic parameters but was potentially attributable to a higher rate of gastrointestinal adverse effects among patients assigned to 1200 or 1600 mg/day, resulting in drug discontinuation and a higher proportion of withdrawals. During a 6-month follow-up, the time to AF relapse increased in dronedarone-treated patients with a median of 60 days compared with 5 days on placebo. At the end of 6 months of follow-up, 35% of patients receiving dronedarone 800 mg/day remained in sinus rhythm (compared with 10% of placebo-treated patients; $p < 0.001$).

EURIDIS and ADONIS were two identically designed prospective trials evaluating efficacy of dronedarone for sinus-rhythm (SR) maintenance including a total of 1237 patients with AF (paroxysmal or persistent) or atrial flutter.[74] Patients were randomized to receive either dronedarone 400 mg or placebo twice daily for 1 year. Combined data from the two trials indicated a median time to the first episode of AF/flutter of 53 days in the placebo group, compared with 116 days in the dronedarone group ($p < 0.0001$). Dronedarone was superior to placebo for AF prophylaxis in a variety of subgroups, including patients with structural heart disease, hypertension, heart failure criteria and previous amiodarone intake.

ANDROMEDA was intended as a survival trial evaluating dronedarone treatment (400 mg twice daily) compared with placebo in patients with symptomatic heart failure and systolic LV

Table IV. Acute effects of dronedarone on action potential parameters

Target	Effect	Species/cell type/conditions	Reference
Atrial APD_{90}	10 μmol/L: ~10% shortening ($p < 0.05$)	Rabbit atrial muscle, recorded at 37 ± 0.5°C	67
Ventricular APD_{90}	10 and 30 μmol/L: ~1% shortening (p = NS)	Guinea-pig papillary muscle recorded at 35 ± 1°C	59
Ventricular APD_{90}	10 μmol/L: ~3–4% prolongation ($p < 0.05$)	Canine papillary muscle (RV) recorded at 37°C, CL 1000 ms	64
Ventricular APD_{90}	30 μmol/L: 3% prolongation (p = NS) 2.5% shortening (p = NS) ~7% prolongation (p = NS)	Canine LV muscle, CL 500 ms Epicardial ventricular cells (LV) M cells (LV) Endocardial ventricular cells (LV)	68
Ventricular APD_{90}	2.5 mg/kg/10 min ~11% shortening (LV, $p < 0.05$) ~6% shortening (RV, p = NS)	Canine chronic AV block, CL 1000 ms, *in vivo* recording of monophasic AP	69
Purkinje APD_{90}	~8% shortening ($p < 0.05$)	Canine Purkinje fibre (LV + RV) recorded at 37°C, CL 1000 ms	64
Sinus node automaticity	10 μmol/L: ~26% increase in sinus cycle length ($p < 0.05$)	Rabbit sinus node cells 37 ± 0.5°C	60

AP = action potential; **APD_{90}** = action potential duration to 90% repolarization; **AV** = atrioventricular; **CL** = cycle length; **LV** = left ventricular; **M cell** = mid-myocardial cell; **NS** = not significant; **RV** = right ventricular.

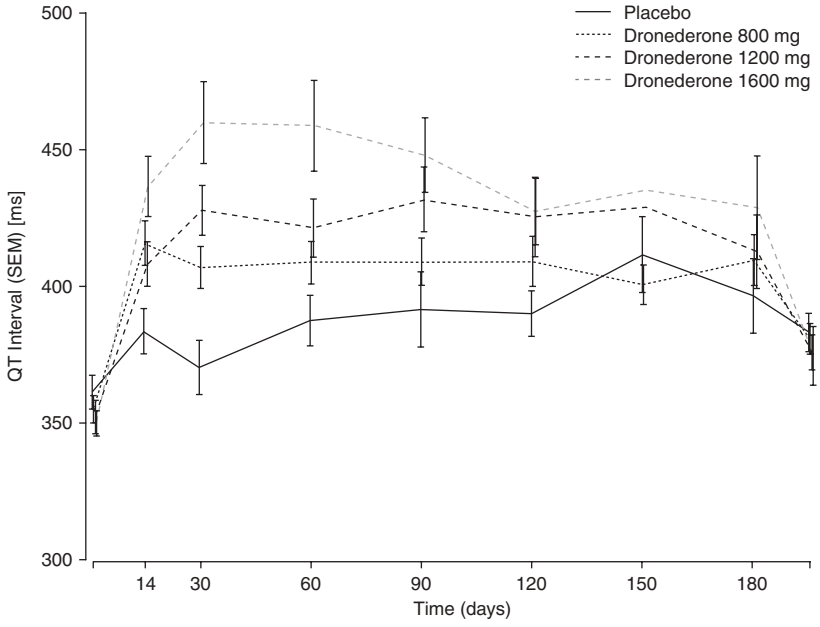


Fig. 3. The effect of dronedarone on QT interval duration in patients with atrial fibrillation. The effects of various active drug concentrations are compared with placebo (reproduced from Touboul et al.,[57] with permission of Oxford University Press). **SEM** = standard error of the mean.

dysfunction (without AF as an enrolment criterion). This trial was prematurely terminated because of increased mortality with dronedarone after the inclusion of 627 patients and a median treatment duration of approximately 2 months.[75] In the dronedarone group, 25 patients (8.0%) had died compared with 12 in the placebo group (3.8%; $p = 0.027$). Deaths were predominantly due to worsening heart failure, and there was no evidence of proarrhythmia or an increased incidence of sudden death in the dronedarone group. After treatment was stopped, subsequent mortality was higher in the cohort that had received placebo and, after 6 months, mortality rates were comparable in both groups (13.5% with dronedarone vs 12.3% with placebo; $p = 0.60$). Increases in the serum creatinine levels were observed more frequently in the active treatment arm. Since dronedarone causes a reversible increase in serum creatinine,[79] this could potentially have been mistaken for ACE inhibitor or angiotensin II type 1 (AT_1) receptor antagonist (angiotensin receptor blockers [ARB]) toxicity. In such cases, physicians tend to interrupt ACE inhibitor treatment, which may, in turn, cause worsening of heart failure. This is one possible explanation for the increased mortality observed with dronedarone therapy in ANDROMEDA. Alternatively, the drug may have a real mortality-enhancing effect in patients with advanced heart failure because of, for example,

Table V. Published clinical trials with dronedarone[a]

Trial[b]	Purpose	Number of patients	Reference
DAFNE	Dose-finding trial	270	57
EURIDIS/ADONIS	Efficacy trials	1237	74
ANDROMEDA	Mortality trial in heart failure	627	75
ERATO	Rate control	174	76
ATHENA	Morbidity and mortality	4628	77
DIONYSOS	Efficacy, active control	504	78

a This table lists five relevant clinical trials of dronedarone published to date. The results of ATHENA and DIONYSOS have not been published as full articles. Overall, 1960 patients were included in these studies demonstrating good tolerability of the dronedarone 400 mg twice daily regimen.

b See table I for full name of trials.

negative inotropic or proarrhythmic complications in this vulnerable population. As a result of this trial, dronedarone is not recommended for use in patients with a history of class III or IV heart failure.

Among dronedarone studies, ERATO was the only trial that enrolled patients with permanent AF to evaluate rate-control properties with dronedarone in addition to standard rate control therapy.[76] Dronedarone significantly reduced mean 24-hour ventricular rate by ~12 beats/minute versus placebo ($p < 0.0001$). This finding was also supported by secondary endpoint analyses of EURIDIS and ADONIS trials, in which dronedarone significantly reduced ventricular rate during the first recurrence of AF/flutter. Mean heart rate was ~102 beats/min and ~105 beats/min in the dronedarone-treatment arms compared with ~118 beats/min ($p < 0.0001$) and ~117 beats/min ($p < 0.0009$) in the placebo arms for EURIDIS and ADONIS, respectively.[74]

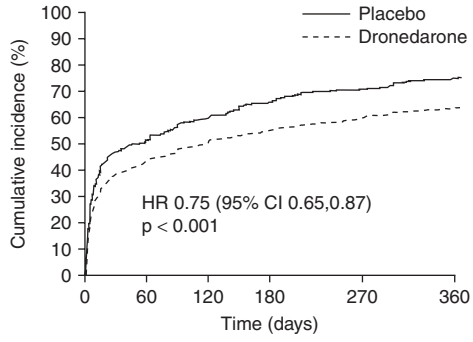
Among the most recently published dronedarone studies are ATHENA and DIONYSOS. ATHENA was completed in January 2008, with the full article published in February 2009.[77] DIONYSOS was completed by the end of 2008. However, details of the results have only been published in the form of a detailed press release, with publication pending.[78]

The ATHENA study included 4628 patients with paroxysmal or persistent AF (or flutter) and was designed as an outcome trial. It is the largest antiarrhythmic drug trial in AF conducted to date and did not specifically examine rates of SR maintenance. Regarding the primary endpoint (death from any cause or cardiovascular hospitalization), ATHENA observed a 24% reduction in the risk of cardiovascular hospitalization or death during a follow-up of ~21 months ($p < 0.001$). The population studied included elderly AF patients (mean age: 72 ± 9 years) with additional risk factors and included nearly 50% women – characteristics similar to those of patients commonly encountered in clinical practice. Interestingly, there were several potentially important findings regarding secondary endpoints. Cardiovascular mortality was reduced by 29% in patients receiving dronedarone ($p < 0.034$) and dronedarone-treated patients were hospitalized less often for cardiovascular reasons (25% less; $p < 0.001$). Of note, the rate of death from cardiac arrhythmia was greatly reduced by dronedarone treatment (45% risk reduction; $p < 0.01$).[77]

2.2.6 Comparison of Clinical Efficacy between Dronedarone and Amiodarone

The DIONYSOS study was designed to compare the efficacy of dronedarone to that of amiodarone and enrolled 504 patients with persistent AF receiving adequate oral anticoagulation with an indication for cardioversion and antiarrhythmic treatment for relapse prevention. The primary endpoint was treatment failure, defined as AF recurrence or premature study drug discontinuation for intolerance or lack of efficacy. Secondary endpoints related to the occurrence of specific adverse effects of amiodarone treatment.[78] Preliminary results were presented in a press release from Sanofi-Aventis in December 2008, which indicated that during a mean follow-up of 7 months 73.9% of dronedarone recipients versus 55.3% of amiodarone recipients reached the primary study endpoint ($p < 0.001$). With respect to AF recurrence, 36.5% of dronedarone-treated patients and 24.3% of amiodarone-treated patients were affected by the end of the trial. Data are not yet fully available, so publication as a full article is still awaited with great interest. In particular, differences in the adverse effect profile will be of interest. However, follow-up was only planned for a minimum period of 6 months and amiodarone toxicity is typically observed later during treatment. Overall, the results available to date support impressions suggesting that dronedarone is substantially better tolerated than amiodarone, but may be somewhat less effective for AF prevention.

Results from EURIDIS and ADONIS showed that the median time to a documented recurrence of AF was 116 days in the dronedarone group (minimum follow-up was 12 months). At 12 months, 64.1% of patients in the dronedarone group had experienced a recurrence of AF (figure 4). In contrast, data from CTAF illustrated that during a mean follow-up of 468 ± 150 days, 35% of patients treated with amiodarone had a recurrence of AF and a median time to



No. at risk

Placebo	409	192	156	133	112	90
Dronedarone	828	450	389	347	307	262

Fig. 4. Efficacy of dronedarone for atrial fibrillation (AF) relapse prevention. Combined Kaplan–Meier cumulative incidence of first AF recurrence in the ADONIS and EURIDIS trials. The hazard ratio (HR) was determined for the dronedarone group compared with placebo (reproduced from Singh et al.,[74] copyright 2007, Massachusetts Medical Society. All rights reserved).

recurrence could not be calculated as more than 50% of patients assigned to amiodarone were still in SR at the end of the trial (figure 5).[37] However, these trials are not directly comparable because patient characteristics and follow-up differed significantly, which is why the DIONYSOS data are awaited with such interest.

2.3 'Upstream' Therapies

Because of the adverse effects and limited efficacy of conventional antiarrhythmic agents, research has focused not only on new antiarrhythmic agents in the classical sense, but also on efforts to prevent development of the AF substrate.[80] A variety of mechanisms contribute to the development of the substrate favouring AF occurrence and maintenance, including neurohormonal activation, tissue inflammation, oxidative stress and electrical remodelling.

2.3.1 Angiotensin Receptor Antagonists and ACE Inhibitors

Drugs interfering with the renin-angiotensin system were among the first compounds tested with respect to their potential efficacy for AF prevention. Experimental studies have shown that inhibition of angiotensin-related signalling pathways can translate into amelioration of the AF substrate.[81] These effects are related to suppression of the conduction abnormalities caused by atrial fibrosis, with beneficial actions on AF not surprising given the importance of heterogeneity of impulse propagation in AF maintenance (section 1.1).

There is a wealth of clinical data available from classical trials that evaluated ACE inhibitors for indications such as hypertension, heart failure and coronary artery disease post-MI.[82,83] Retrospective analyses of these trials consistently indicate protective effects of ACE-inhibitor treatment with respect to AF development.[3] Data from the more recent LIFE trial indicated reductions in AF occurrence for losartan- versus atenolol-treated patients.[84] ARBs reduced cardiovascular morbidity and mortality and stroke risk in hypertensive patients with previous AF.[84] Presently available data have two shortcomings: (i) none of these studies evaluated incidence of AF as a predefined primary endpoint; and (ii) data were obtained from patient populations at risk of AF development with an indication for ACE-inhibitor treatment. Data from a small recent trial indicated efficacy of ACE inhibitor treatment for prevention of AF relapses in patients with lone AF.[85] In this study, 62 patients with lone AF were randomized (1 : 1) to receive either ramipril or placebo and were followed-up for 3 years. During this period 3 of 31 patients assigned to ramipril and 10 of 31 patients assigned to placebo developed AF observed on holter monitoring ($p < 0.05$),

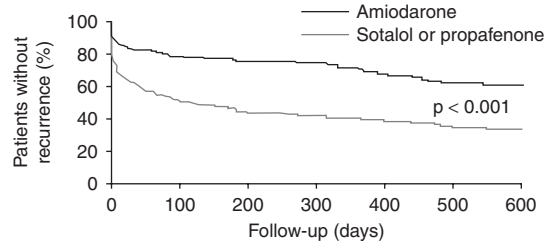


Fig. 5. Efficacy of amiodarone for atrial fibrillation (AF) relapse prevention. Kaplan–Meier estimates of the percentage of patients remaining free of AF relapse for patients treated with amiodarone (n = 201) compared with those receiving sotalol or propafenone (n = 202) [hazard ratio for recurrence among patients in the amiodarone group 0.43; 95% CI 0.32, 0.57]. Reproduced from Roy et al.,[37] copyright 2000, Massachusetts Medical Society. All rights reserved.

indicating efficacy in reducing AF relapses even in the absence of a classical indication for ACE inhibitor treatment.

Another line of evidence points towards a potential protective role of ACE inhibitors for AF relapse prevention. Retrospective analysis of rhythm-control patients within AFFIRM indicated fewer AF relapses in ACE-inhibitor-treated patients with CHF.[86] This has been prospectively addressed by adding irbesartan to amiodarone treatment after electrical cardioversion, leading to reduced AF recurrences in irbesartan-treated patients.[87] Consistent results were obtained in another study that evaluated an ACE inhibitor in addition to amiodarone.[88] In these trials, a combination of renin-angiotensin system inhibition with efficient antiarrhythmic therapy led to an improved outcome in terms of freedom from arrhythmia relapse, albeit over a relatively short timeframe.

The ACTIVE trial, primarily comparing aspirin (acetylsalicylic acid) plus clopidogrel versus conventional anticoagulation with warfarin AF patients, has a study arm comparing patients treated with irbesartan versus placebo and will be the first prospective study to provide information with respect to ARB use in AF.[89] Another ongoing trial (ANTIPAF) is studying olmesartan in patients with paroxysmal AF.[90] The recently completed GISSI-AF trial,[91] results of which have thus far been reported only in abstract form, failed to confirm benefit in AF of the addition of the ARB valsartan to conventional management, including amiodarone and ACE inhibitors.

2.3.2 HMG-CoA Reductase Inhibitors and Immunosuppressive Agents

Atrial tissue fibrosis is particularly important in the pathophysiology of AF associated with heart failure. Experimental data indicate effective reduction in CHF-related structural remodelling and AF promotion by simvastatin. In addition, simvastatin improved haemodynamic function and inhibited atrial fibroblast activation.[92] Clear evidence of corresponding clinical benefit is lacking, but the inherent anti-inflammatory properties of HMG-CoA reductase inhibitor (statin) therapy may confer protection against AF in some subgroups, particularly patients undergoing cardiothoracic surgery.[93] Glucocorticosteroid treatment prevents the development of a substrate for AF in animal models.[94,95] Clinical data point to potential efficacy of glucocorticosteroids in AF prevention;[96,97] however, because of associated risks, such an approach would have to be applied very carefully.

The overall value of these attractive 'upstream therapeutic' approaches will have to be clarified in prospective randomized trials (currently ongoing). The interested reader is referred to a recent detailed review of this complex area.[98]

3. Potential Impact of Ablation Procedures on use of Drug Therapy for AF

Drug treatment remains the mainstay of therapy for most patients despite continuous improvement of ablation techniques. In general, ablation is recommended for patients with paroxysmal AF, ideally younger than 60 years of age with near-normal left atrial size and LV systolic function.[99] Ablation therapy is usually considered only after antiarrhythmic drugs have failed, because catheter ablation is an invasive procedure with attendant potential risks, including procedural stroke and pulmonary vein stenosis.[99]

The concept of successful ablation of ectopic activity for AF carries the potential of treating AF patients without the need for adjunctive medical therapy. Since the original description, the technique has been modified from ablation within the pulmonary veins towards the encircling and electrically isolating of all pulmonary vein ostia.[99] Few randomized comparisons of ablation therapy with antiarrhythmic drug treatment exist that analyzed time to AF recurrence and quality of life as primary endpoints.[100]

The first clinical trial comparing ablation to drug therapy for AF in a randomized fashion found that at the end of a 1-year follow-up, 22 (63%) of 35 patients who received antiarrhythmic drugs had at least one recurrence of symptomatic AF compared with 4 (13%) of 32 patients who received pulmonary vein isolation ($p < 0.001$).[101] Pappone and colleagues[102] reported results obtained from almost 200 patients with paroxysmal

AF who had been randomized to ablation or treatment with amiodarone, flecainide or sotalol, either as single drugs or in combination at the maximum tolerable dosages. By Kaplan-Meier analysis, 86% of patients in the ablation group and 22% of those in the medical treatment group were free from recurrent atrial tachyarrhythmias ($p < 0.001$). At 1 year, 93% and 35% of the ablation and drug therapy groups, respectively, were free from AF recurrence.

While these two trials studied patients assigned to interventional therapy alone versus antiarrhythmic drug treatment, another study evaluated ablation in addition to medical therapy. Results reported by Stabile et al.[103] in a study of ~140 patients with paroxysmal AF were consistent with the previously mentioned studies. After 12 months of follow-up, 91.3% of patients assigned to antiarrhythmic drug treatment alone had at least one AF recurrence, whereas 44.1% ($p < 0.001$) of ablation group patients had atrial arrhythmia recurrence. The type and distribution of antiarrhythmic drug therapy was not different between groups.

There is presently no randomized prospective study comparing survival as an outcome for patients with AF undergoing ablation therapy with patients treated with conventional antiarrhythmic drugs.[100]

There is a consensus that AF ablation is indicated for many patients with paroxysmal AF, but there is a lack of larger-scale, prospective, randomized trials of interventional versus antiarrhythmic drug treatment.[99] Although recent data suggest a wider role for ablation, including use as first-line therapy in selected patients and potential value in improving LV dysfunction associated with AF, the size of the AF population and limitations in efficacy and safety of ablation procedures suggest that drug approaches will continue to play an important role in the management of the arrhythmia for the foreseeable future.[104]

4. Conclusions

AF is a growing medical problem and improved therapeutic approaches are needed. Although attempts to cure AF by catheter ablation are being made, it remains questionable whether this technique will ever be applicable to the majority of patients. Accordingly, improved pharmacological therapies are needed and are currently being developed. Vernakalant and dronedarone are two novel antiarrhythmic drugs that may provide improved therapeutic options. Substrate-targeted 'upstream therapies' such as inhibitors of the angiotensin system or statins have interesting potential, but it is too early to know whether this will translate into effective AF treatment modalities. It is likely that various forms of AF therapy will optimally be tailored to specific patient populations. This is an area of major ongoing investigation, which provides hope for major improvements in AF management over the next decade.

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