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*Europace* 10:647-665, 2008.

doi:10.1093/europace/eun130

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## REVIEW

# Anti-arrhythmic drug therapy for atrial fibrillation: current anti-arrhythmic drugs, investigational agents, and innovative approaches

Irina Savelieva\* and John Camm

*Division of Cardiac and Vascular Sciences, St George's University of London, Cranmer Terrace, London SW17 0RE, UK*

Received 29 February 2008; accepted after revision 25 April 2008

### KEYWORDS

Atrial fibrillation;  
Anti-arrhythmic drugs;  
Rhythm control;  
Atrial repolarization-delaying agents;  
Dronedaronone;  
Vernakalant;  
Gap junction modifiers;  
Rotigaptide

By 2050, atrial fibrillation (AF) will be present in 2% of the general population and in a far higher proportion of elderly patients. Currently, we are content with rate control and anticoagulation in elderly asymptomatic patients, whereas in younger patients with symptomatic recurrent AF, pulmonary vein isolation is the treatment of choice. However, in a large number of patients, there remains a genuine choice between anti-arrhythmic therapy to suppress the arrhythmia and rate control to control the ventricular rate. This review provides a contemporary evidence-based insight into the buoyant development of new anti-arrhythmic agents, exploring new mechanisms of action or novel combinations of established anti-arrhythmic activity.

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. Presently, there are several potential anti-arrhythmic drugs with this mode of action, which are currently in pre-clinical and clinical development. Vernakalant is in the most advanced phase of investigation and its intravenous formulation has recently been recommended for approval for pharmacological cardioversion of AF. However, although this agent has some electrophysiological effects which are specific to the atria, it has others which affect both the atria and the ventricles. Other drugs, such as XENDO101, block a single atrial-specific membrane current. The success of such agents depends critically on their atrial electrophysiological selectivity, freedom from cardiac adverse effects, and general safety.

Other possibilities include modified analogues of traditional anti-arrhythmic drugs with additional novel mechanisms of action and less complex metabolic profiles. Dronedaronone is an investigational agent with multiple electrophysiological effects, which is devoid of iodine substituents and is believed to have a better side effect profile than its predecessor amiodarone. The development portfolio of dronedaronone is practically complete and approval for several indications in AF may soon be assessed.

Innovative anti-arrhythmic agents with unconventional anti-arrhythmic mechanisms, such as stretch receptor antagonism, sodium-calcium exchanger blockade, late sodium channel inhibition, and gap junction modulation, have not yet reached clinical studies in AF. Gene- and cell-based therapies, which can selectively target individual currents, could provide ideal one-time only curative therapy for arrhythmias, and the first proof-of-concept studies have been reported.

There is accumulating evidence in support of the anti-arrhythmic effects of non-anti-arrhythmic drugs. Treatments with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, statins, and omega-3 fatty acids all seem promising, over and above any effect related to the treatment of underlying heart disease. However, despite exciting results from animal experiments and promising outcomes from retrospective analyses, there is no robust evidence of specific effects of these drugs to transform current clinical practice.

## Introduction

Atrial fibrillation (AF) has a broad variety of presentations and demands a range of therapeutic responses. Sudden-onset, sustained, symptomatic arrhythmia requires

\* Corresponding author. Tel: +44 20 8725 0439; fax: +44 20 8767 7141.  
E-mail address: isavelie@sghs.ac.uk; isavelie@sghms.ac.uk

termination (cardioversion), recurrent AF needs prophylactic therapy to prevent or reduce recurrences, and permanent or accepted AF warrants ventricular rate control. Pharmacological therapy is applied to all situations and multiple anti-arrhythmic drugs have been licenced for each of these indications but the efficacy of these agents remains suboptimal, especially in the long term, and individual proarrhythmic risk and toxic effects are poorly predictable.

The recent publication of several studies which compared rhythm control (cardioversion and subsequent prophylactic therapy against recurrence) with rate control led to the conclusion that rhythm control is not superior to rate control; furthermore, that rhythm control is more costly and inconvenient than rate control.<sup>1</sup> This has not affected the application of rhythm control treatment to patients who are highly symptomatic, patients with recent-onset AF, or young patients, but 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. However, it is very likely that better (safer and more effective) anti-arrhythmic therapy would reverse this trend away from rhythm control. Intuitively rhythm control is preferred, but now cannot be achieved without hazard.

Some forms of AF may be treated non-pharmacologically with catheter-based pulmonary vein ablation or isolation, surgically based maze operations, and atrioventricular node ablation for rate control. The American College of Cardiology/American Heart Association/European Society of Cardiology guidelines on management of AF updated in 2006 have upgraded pulmonary vein ablation to the second choice after one anti-arrhythmic drug has failed.<sup>2</sup> The eventual impact of pulmonary vein isolation is not yet known. At present, it is likely to be successfully used in younger individuals with refractory paroxysmal AF and near-normal hearts, but several reports from experienced centres have suggested that patients with more advanced heart disease, e.g. heart failure, particularly when tachycardia-induced cardiomyopathy is suspected, may benefit from left atrial ablation.<sup>3</sup> The surgical maze procedure is presently limited to patients undergoing other heart surgery, e.g. mitral valve repair or replacement. However, as these operations become minimally invasive and highly effective, they are likely to be more widely used.<sup>4</sup> Ablation of the atrioventricular node in conjunction with implantation of a permanent pacemaker is not a popular strategy and is used in only 1–2% of the group with permanent AF and poor pharmacological rate control.

### Current anti-arrhythmic drug therapy

Anti-arrhythmic drugs have been traditionally defined as membrane-active agents which modulate the opening and closing of ion channels, change the function of membrane pumps, and activate or block membrane receptors. In electrophysiological terms, such drugs may essentially increase refractoriness of the myocardium, decrease conduction velocity through the myocardium or completely block conduction at vulnerable points, and decrease the firing rate of automatic focal discharges. But a potentially valuable combination of these effects may only be achieved at appropriate concentrations in damaged tissue, with normal electrolyte and acid–base balance, and at certain underlying heart rates. In less favourable circumstances, for example,

at the wrong concentration, in less abnormal tissue, at slower heart rates, or in a different milieu, the drug may not only fail to be anti-arrhythmic but may also be proarrhythmic.

Theoretically, an ideal anti-arrhythmic drug for AF would safely (without producing ventricular proarrhythmia) and effectively terminate and prevent the recurrence of AF in patients with and without structural heart disease, would not exert negative inotropic effect or interfere with thrombo-embolic prophylaxis, and would provide rate control (atrioventricular node blockade) during the recurrence of AF. Although currently available anti-arrhythmic drugs may theoretically satisfy several of these criteria, in practice, none is sufficiently effective and/or safe in the diverse settings in which AF occurs. *Table 1* illustrates how most popular anti-arrhythmic drugs comply with these criteria. Amiodarone is the single most effective agent for all three indications and has a neutral effect on all-cause mortality.<sup>5</sup> In the recent Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), amiodarone was superior to sotalol and placebo in maintaining sinus rhythm in 665 patients with persistent AF.<sup>6</sup> The median times to a recurrence of AF were 487 days in the amiodarone group, 74 days in the sotalol group, and 6 days in the placebo group, according to intention to treat and 809, 209, and 13 days, respectively, according to treatment received. However, amiodarone is not a rapidly effective or convenient drug for cardioversion and its use as an atrioventricular node-blocking agent for ventricular rate control is not sensible because of a very adverse risk–benefit ratio. Flecainide, propafenone, and ibutilide are popular for pharmacological cardioversion and have been specifically licenced for that purpose in some parts of Europe (flecainide and propafenone) and North America (ibutilide), but none of these drugs is highly effective and safe outside the setting of recent-onset AF in patients with essentially normal hearts.<sup>2</sup>

$\beta$ -Blockers, generally, are only modestly effective as an anti-arrhythmic strategy in AF, with exception of adrenergically mediated AF or AF caused by thyrotoxicosis. In a recent meta-analysis, therapy with  $\beta$ -blockers was associated with a 27% reduction in the incidence of new-onset AF (from 39 to 28 per 1000 patient-years) in the setting of systolic heart failure—the effect which is likely to be due to the overall beneficial effect of  $\beta$ -blockade on the left ventricle.<sup>7</sup> Carvedilol, in addition to its anti-adrenergic effects and membrane-stabilizing activity, inhibits the rapidly activating delayed rectifier current ( $I_{Kr}$ ) at concentrations similar to those observed in a clinical setting.<sup>8</sup> At higher concentrations, carvedilol blocked the L-type calcium current ( $I_{CaL}$ ), the transient outward current ( $I_{to}$ ), and, to a lesser extent, the slowly activating component of the activating delayed rectifier current ( $I_{Ks}$ ).<sup>8</sup> In a small prospective study in 49 patients with persistent AF, carvedilol 12.5–50 mg once daily had a similar conversion rate to a standard loading and maintenance dose of amiodarone, but was less effective than amiodarone in maintaining sinus rhythm.<sup>9</sup>

### Novel anti-arrhythmic drug strategies

Innovative strategies targeting different mechanisms of AF development and maintenance have been explored (*Figure 1*).<sup>10</sup> Novel anti-arrhythmic drugs with conventional anti-arrhythmic mechanisms are under investigation in AF,

**Table 1** Comparison of anti-arrhythmic and cardiovascular effects of approved anti-arrhythmic drugs for atrial fibrillation

Drug	Route	Acute conversion (%)	Rhythm control	Rate control	Efficacy in sinus rhythm maintenance (%)	Normal heart	Heart disease	Inotropic effect	Warfarin interaction	Proarrhythmic potential
Procainamide	IV	51–70	No	No	–	3rd choice	Contraindicated	Negative	–	QRS widening and ventricular tachycardia
Flecainide	IV and oral	59–78	Yes	No	70–80	1st choice	Contraindicated	Negative	No	1:1 AV conduction
Propafenone	IV and oral	51–72	Yes	No	65–75	1st choice	Contraindicated	Negative	No	1:1 AV conduction
Sotalol	IV and oral	11–13	Yes	Occasionally used	37–74	2nd choice	1st choice	Neutral	No	Bradycardia, prolonged QT, and torsades
Ibutilide	IV	31–51 <sup>a</sup> and 63–73 <sup>b</sup>	No	No	–	Yes	Yes	Neutral	–	Prolonged QT and torsades
Dofetilide	Oral <sup>c</sup>	29 <sup>d</sup>	Yes	No	58 <sup>a</sup> and 73 <sup>b</sup>	3rd choice	2nd choice	Neutral	Promote	Prolonged QT and torsades
Amiodarone	IV and oral	44	Yes	Occasionally used	65	3rd choice	1st choice	Neutral	Promote	Multiorgan toxicity

<sup>a</sup>In atrial fibrillation; <sup>b</sup>in atrial flutter; <sup>c</sup>intravenous formulation has been studied (24% conversion rate in atrial fibrillation and 64% in atrial flutter), but is not currently used in practice; <sup>d</sup>1000 mcg; AV, atrioventricular; IV, intravenous.

including newer multiple-channel blockers with a better safety profile and specific agents targeting atrial repolarization (Figure 2). Agents with unconventional modes of action are envisioned, such as stretch receptor antagonists, blockers of the sodium–calcium exchanger, late sodium channel inhibitors, and gap junction modulators, which may improve ‘the communication’ between cells.<sup>10</sup> ‘Upstream’ therapies with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), statins, and omega-3 polyunsaturated fatty acids (PUFAs) have theoretical advantages as potential novel therapeutic strategies.<sup>11,12</sup>

### Newer and investigational class III compounds

Numerous class III or repolarization-delaying compounds have been partly developed and then abandoned, largely because of the risk of torsades de pointes brought about by the effect of ventricular repolarization (Table 2).

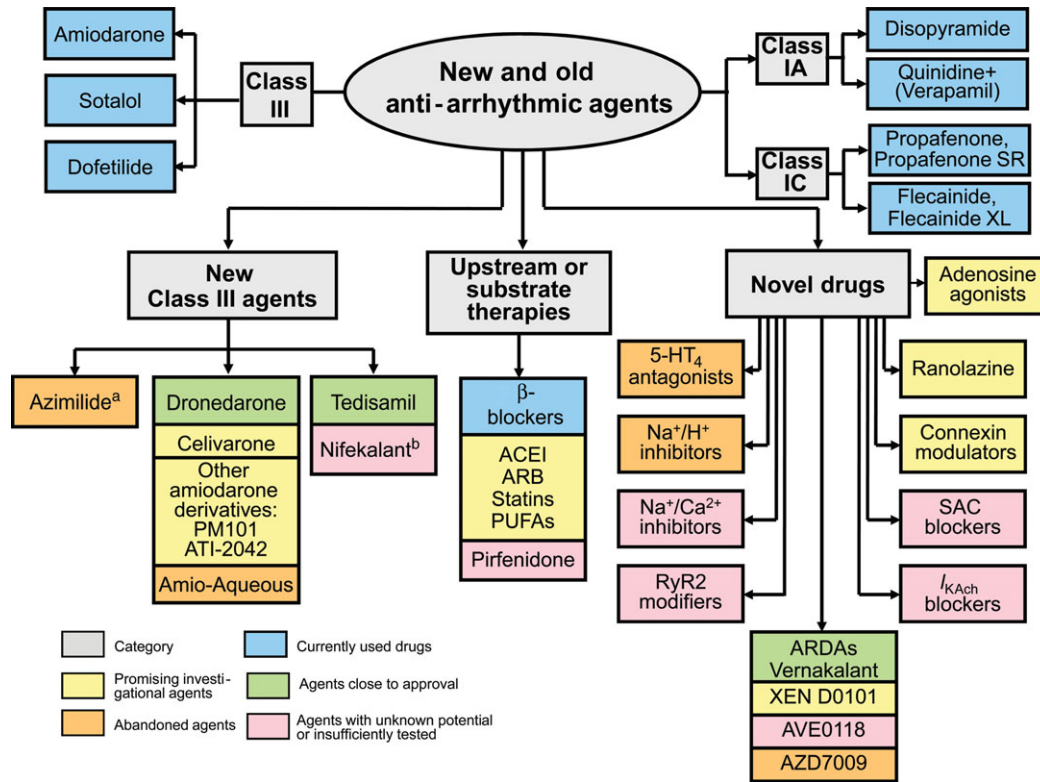
#### Azimilide

*Azimilide* (Procter & Gamble) blocks both  $I_{Kr}$  and  $I_{Ks}$  currents and therefore is expected to be particularly effective during high rates associated with AF than pure  $I_{Kr}$  blockers. This is because during rapid heart rates, the contribution of  $I_{Kr}$  to repolarization is functionally diminished because of the enhanced contribution of other currents, such as  $I_{Ks}$ , which accumulate at faster rates as a result of incomplete deactivation. Although initial studies in AF were encouraging,<sup>13,14</sup> later post-cardioversion maintenance of sinus rhythm studies and all-comers maintenance programmes showed less impressive results. The ALIVE (Azimilide Post-Infarct Survival Evaluation) trial of 3717 patients with a recent myocardial infarction and left ventricular dysfunction has shown a neutral effect of azimilide on all-cause mortality, including patients with a significantly reduced ejection fraction.<sup>15</sup> Fewer patients who started the trial in sinus rhythm developed AF on azimilide and there was a trend to higher pharmacological conversion rates in the azimilide arm than in the placebo arm (26.8 vs. 10.8%).<sup>16</sup>

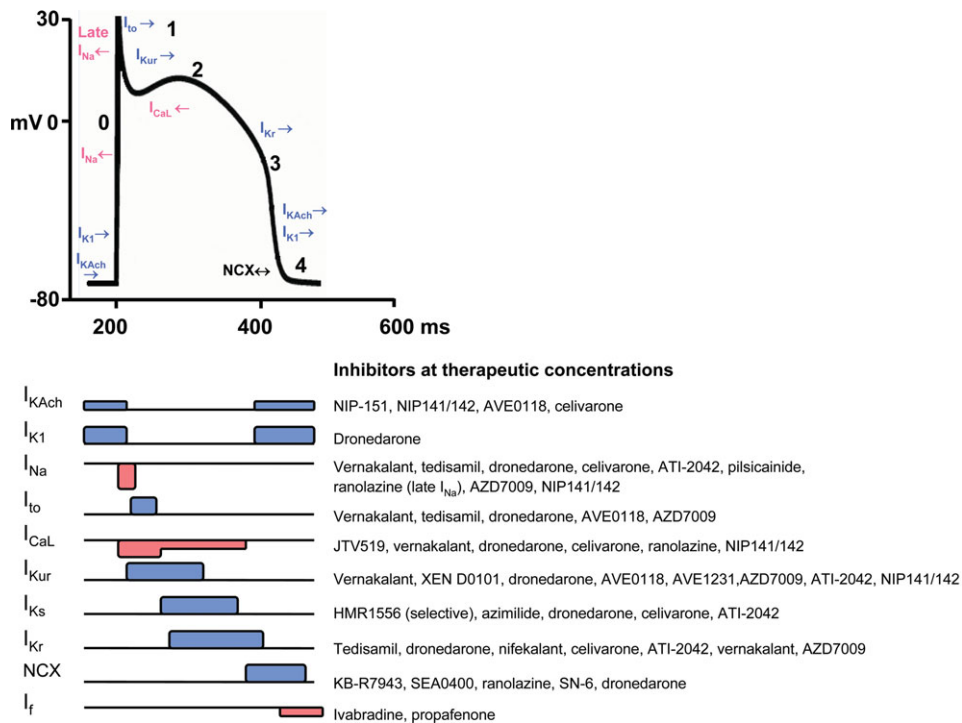
Several studies in patients with persistent AF, A-STAR (Supraventricular TachyArrhythmia Reduction), and A-COMET I and II (CardioVersion Maintenance Trial) have failed to show any anti-arrhythmic benefit of azimilide<sup>17–19</sup> and some unveiled torsadogenic potential.<sup>20</sup> The marginal efficacy, which was restricted to patients with structural heart disease seen with azimilide, is a limitation and hence it is doubtful that azimilide will claim a place for the treatment of AF.

#### Tedisamil

*Tedisamil* (Solvay) produces multiple potassium channel blockade, including  $I_{Kr}$ ,  $I_{to}$ , and  $I_{KATP}$  and a negative chronotropic effect by increasing gap junctional conductance and conduction velocity, which may prevent fast ventricular rates during AF recurrence. Unlike selective  $I_{Kr}$  blockers, tedisamil is devoid of reverse use-dependence with respect to atrial refractoriness. Tedisamil has been abandoned as a long-term medication because of diarrhoea due to blockade of the potassium current in the intestine and consequent hypokalaemia and torsades de pointes, but is currently under investigation for acute pharmacological cardioversion in AF. In a dose-efficacy study in 175 patients



**Figure 1** Currently available, investigational, and experimental anti-arrhythmic agents for atrial fibrillation. <sup>a</sup>Azimilide is not used for the treatment of atrial fibrillation; its use in patients with implantable defibrillators is under consideration. <sup>b</sup>Nifekalant is used in Japan, mainly for the termination of ventricular tachycardia. ACEI, angiotensin-converting enzyme inhibitors; angiotensin type I receptor blockers; ARDA, atrial repolarization-delaying agents; HT, hydroxytryptamine; PUFA, polyunsaturated fatty acids; RyR, ryanodine receptors; SAC, stretch-activated channels.



**Figure 2** Ion currents determining the atrial action potential and the occurrence of each current in relation to the action potential. Arrows pointing to the left and downwards rectangles (red) indicate inward currents; arrows pointing to the right and upright rectangles (blue) indicate outward currents. The majority of new anti-arrhythmic agents block several ion currents; blocks that occur at therapeutic concentrations are shown.

**Table 2** Investigational repolarization prolonging agents

Agent	Mechanism of action	Route	Current status	Potential in AF
Azimilide	$I_{Ks}$ and $I_{Kr}$ blocker	Oral	Not approved for AF	Prevention, moderate
Dronedarone	Multiple-channel blocker	Oral	Phase III	Prevention, moderate
Amiodarone Aqueous	Soluble amiodarone	IV	Phase II, development halted	Conversion
PM101	Captisol-enabled soluble amiodarone	IV	Phase I	Conversion
ATI-2042	Multiple-channel blocker	IV	Phase II	Prevention
Tedisamil	$I_{Kr}$ and $I_{to}$ blocker	IV	Phase III	Conversion
		Oral	Abandoned	Prevention
Nifekalant (MS-551)	$I_{Kr}$ blocker	IV	Limited studies	Insufficient data
Ambasilide (LU 47110)	Multiple-channel blocker	Oral and IV	Suspended	Insufficient data
Ersentilide	$I_{Kr}$ and $\beta_1$ blocker	Oral and IV	Abandoned	Unknown
Trecetilide	$I_{Kr}$ and $I_{Na}$ blocker	Oral and IV	Abandoned	Unknown
Almokalant	$I_{Kr}$ blocker	IV	Abandoned	Insufficient data
D-Sotalol	$I_{Kr}$ blocker	Oral	Abandoned	Prevention, moderate
BRL-32872	$I_{Kr}$ and $I_{CaL}$ blocker	Oral and IV	Abandoned	Prevention, moderate
HMR1556 (chromanols)	$I_{Ks}$ blocker	IV	Experimental	Unknown
L768673 (benzodiazepines)	$I_{Ks}$ blocker	IV	Experimental	Unknown

AF, atrial fibrillation; IV, intravenous.

with little structural heart disease and recent-onset AF, tedisamil 0.4 and 0.6 mg/kg restored sinus rhythm in 41 and 51% of the patients, respectively, compared with 7% in the placebo arm.<sup>21</sup> However, two patients who received the highest dose developed ventricular tachycardia. On the whole, because of its modest efficacy and high proarrhythmic risk, tedisamil is unlikely to be a useful remedy for AF, and it has not been granted an approval from FDA.

### Nifekalant

*Nifekalant* is a reverse use-dependent  $I_{Kr}$  blocker which is used in Japan for the acute treatment of ventricular tachyarrhythmias refractory to other anti-arrhythmic drugs. It prolonged the atrial effective refractory period and terminated atrial flutter in 75% of the patients within 1 h, but was ineffective in converting AF.<sup>22</sup>

### Dronedarone

*Dronedarone* (sanofi aventis) is an investigational agent with multiple electrophysiological effects, which is similar to amiodarone, but it is devoid of iodine substituents and is believed to have a better side effect profile. In experimental studies, using the whole-cell patch-clamp technique applied to human atrial myocytes, dronedarone inhibited transmembrane potassium currents: ultrarapid-delayed rectifier ( $I_{Kur}$ ), delayed rectifier ( $I_{Ks}$  and  $I_{Kr}$ ), transient outward ( $I_{to}$ ), and inward rectifier ( $I_{K1}$ ).<sup>23</sup> The anti-arrhythmic potential of dronedarone has been extensively studied. A dose-finding study and two middle size efficacy and safety trails have been published in full; the results of large mortality trials are expected shortly (Table 3). EURIDIS (EUropean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm) and its American–Australian–African equivalent ADONIS have shown that dronedarone 400 mg twice daily ( $n = 828$ ) was superior to placebo ( $n = 409$ ) in prevention of recurrent AF and was also effective in controlling ventricular rates.<sup>24</sup> In the European trial, the median time

to the recurrence of arrhythmia (the primary endpoint) was 41 days in the placebo group and 96 days in the dronedarone group ( $P = 0.01$ ). In the American–Australian–African counterpart, the corresponding time was 59 and 158 days ( $P = 0.002$ ). The superiority of dronedarone over placebo was consistent in all pre-specified patients groups, such as patients with and without structural heart disease, hypertension, heart failure, the left atrial size dichotomized at 4 cm, and the presence or absence of the previous use of amiodarone. Dronedarone did not significantly prolong the QT interval and probably has a low potential for causing torsades de pointes.<sup>23</sup> However, as with amiodarone, there may be some risk of pulmonary fibrosis, ocular side effects, and skin photosensitivity, although very substantially less than with amiodarone.

In EURIDIS and ADONIS, the ventricular rates during the recurrence of AF were on average 12–15 b.p.m. lower in the dronedarone arm than in the placebo arm. The ability of the drug to control ventricular rates was prospectively assessed in the ERATO (Efficacy and Safety of Dronedarone for the Control of Ventricular Rate) study of 174 patients with permanent AF and a resting heart rate of  $>80$  b.p.m., despite standard therapy with  $\beta$ -blockers, calcium antagonists, and digitalis.<sup>25</sup> Patients treated with dronedarone had the mean 24-h ventricular rates after 14 days of treatment (the primary endpoint of the study) 12 b.p.m. lower compared with those who received placebo. In addition, dronedarone limited the peak heart rate during a maximal symptom-limited exercise test by 24 b.p.m. compared with placebo, without affecting the overall exercise capacity.

EURIDIS and ADONIS were not designed to assess mortality and excluded patients with significant left ventricular dysfunction. The ANDROMEDA (ANTI-arrhythmic trial with DRonedarone in Moderate to severe heart failure Evaluating morbidity Decrease) study was initiated to explore the effects of dronedarone on all-cause death and hospitalizations for heart failure in patients with New York Heart Association function class III or IV heart failure. The trial was, however, stopped prematurely

**Table 3** Summary of clinical studies of dronedarone in atrial fibrillation

Study	Number of patients	Patient characteristics	Dose of dronedarone	Placebo controlled	Primary endpoint	Follow-up, months	Outcome	Comments
DAFNE	199	Post-cardioversion	400 mg b.i.d. 600 mg b.i.d. 800 mg b.i.d.	Yes	Time to first AF recurrence	6	Dronedarone 400 mg b.i.d. significantly prolonged median time to first AF recurrence vs. placebo: 60 vs. 5.3 days, $P = 0.026$ ; relative risk reduction 55% (95% CI, 28–72% $P = 0.001$ )	Higher doses were ineffective and were associated with discontinuation rates of 7.6 and 22.6%; conversion rates were 5.8, 8.2, and 14.8% vs. 3.1% on placebo
EURIDIS	615	Post-cardioversion	400 mg b.i.d.	Yes	Time to first AF recurrence	12	Median time to first AF recurrence was 41 days on dronedarone vs. 96 days on placebo, $P = 0.01$	Ventricular rates during AF recurrence were significantly lower on dronedarone
ADONIS	630	Post-cardioversion	400 mg b.i.d.	Yes	Time to first AF recurrence	12	Median time to first AF recurrence was 59 days on dronedarone vs. 158 days on placebo, $P = 0.002$	Dronedarone reduced ventricular rates during AF recurrence vs. placebo
EURIDIS and ADONIS pooled	1237	Post-cardioversion	400 mg b.i.d.	Yes, $n = 409$	All-cause mortality and hospitalizations <sup>a</sup>	12	Dronedarone reduced the primary endpoint vs. placebo by 27% (95% CI, 7–43%, $P = 0.01$ )	Trend towards reduced all-cause mortality and hospitalizations from cardiac causes was observed with dronedarone; relative risk reduction 20%, $P = 0.164$
ERATO	630	Permanent AF with ventricular rates >80 b.p.m. on rate-controlling therapy	400 mg b.i.d.	Yes	Mean 24-h ventricular rate at 2 weeks	1	Ventricular rates were 12 b.p.m. lower on dronedarone vs. placebo	Peak heart rates during exercise were 24 b.p.m. lower on dronedarone vs. placebo
ANDROMEDA	617, 1000 planned	Congestive heart failure; EF < 0.35	400 mg b.i.d.	Yes	All-cause mortality	6	Stopped early because of increased mortality in the dronedarone arm (8 vs. 3.8% on placebo; hazard ratio 2.3)	Possible explanation for increased mortality is more frequent discontinuation of ACE inhibitors in the dronedarone arm secondary to an increase in plasma creatinine
ATHENA	4628	Paroxysmal or persistent AF with risk factors	400 mg b.i.d.	Yes	All-cause mortality and hospitalizations for cardiac causes	21 ± 5	Dronedarone reduced the primary endpoint vs placebo by 24% ( $P < 0.001$ )	Cardiovascular hospitalizations, cardiovascular mortality, and hospitalizations for AF were reduced by 25% ( $P < 0.001$ ), 29% ( $P = 0.034$ ), and 37% ( $P < 0.001$ ); no significant difference in all-cause mortality

ACE, angiotensin-converting enzyme; ADONIS, American–Australian–African trial with dronedarone in atrial fibrillation or flutter for the maintenance of sinus rhythm; AF, atrial fibrillation; ANDROMEDA, anti-arrhythmic trial with dronedarone in moderate to severe heart failure evaluating morbidity decrease; ATHENA, a placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter; b.p.m., beats per minute; DAFNE, dronedarone atrial fibrillation study after electrical cardioversion; EF, ejection fraction; ERATO, efficacy and safety of dronedarone for the control of ventricular rate; EURIDIS, European trial in atrial fibrillation or flutter patients receiving dronedarone for the maintenance of sinus rhythm. <sup>a</sup>post hoc analysis.

after 627 patients out of the 1000 planned were enrolled, because an interim safety analysis revealed a potential excess risk of death in patients on active treatment: 25/310 (8%) vs. 12/317 (3.8%) on placebo [hazard ratio 2.13, 95% confidence intervals (CIs), 1.07–4.25,  $P = 0.027$ ; data were presented at the Congress of the European Society of Cardiology in Stockholm in 2006]. The adverse outcome of ANDROMEDA is thought to be due to an increase in creatinine in the dronedarone arm, which prompted inappropriate discontinuation of potentially life-saving therapy with ACE inhibitors. Dronedarone inhibits tubular absorption of creatinine and therefore has the potential to increase plasma creatinine, which may be an issue of concern in some patients.

Nevertheless, the *post hoc* analysis of the EURIDIS and ADONIS studies showed that among patients treated with dronedarone, fewer were hospitalized for cardiovascular causes or died than in the placebo group (22.8 vs. 30.9%; hazard ratio 0.73, 95% CI, 0.57–0.93,  $P = 0.01$ ).<sup>24</sup> This observation has been further explored in a phase III randomized controlled study ATHENA (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENTs with Atrial fibrillation/atrial flutter) which enrolled 4628 high-risk patients<sup>26</sup>. Mean follow-up was  $21 \pm 5$  months. The results of the ATHENA trial were reported at the Heart Rhythm Society's Annual Scientific Sessions in May 2008. Dronedarone prolonged time to first cardiovascular hospitalization or death from any cause (the composite primary endpoint) by 24% ( $P < 0.001$ ) compared with placebo. This effect was driven by the reduction in cardiovascular hospitalizations (25%), particularly hospitalizations for AF (37%). All-cause mortality was similar in the dronedarone and placebo groups (5% and 6%, respectively; hazard ratio 0.84, 95% CI, 0.66–1.08,  $p = 0.176$ ); however, dronedarone significantly reduced deaths from cardiovascular causes. Thus, the development portfolio of this drug is practically complete and approval for several indications concerning AF may soon be assessed.

## Other amiodarone derivatives

### Celivarone

Sanofi aventis has a clutch of other amiodarone/dronedarone analogues at various stages of development. Information on *celivarone* (SSR149744C), a non-iodinated benzofurane derivative which exhibits multiple channel-blocking properties and haemodynamic effects, has recently been reported. The drug is available in both intravenous and oral forms and has been demonstrated to terminate vagally induced AF in dogs in 100% of the experiments and to prevent induction of AF in 60% of the experiments.<sup>27</sup> The safety and efficacy of SSR149744C for the maintenance of sinus rhythm has been studied in a phase II dose-ranging study, MAIA (MAintenance of sinus rhythm In patients with recent Atrial fibrillation of flutter), in 673 patients who were randomized to one of four doses (50, 100, 200, or 300 mg once daily) or placebo.<sup>28</sup> The primary endpoint was the recurrence of the arrhythmia detected by an electrocardiogram (ECG) and transtelephonic ECG monitoring. As with dronedarone, the higher doses of celivarone tended to be less effective than the lower doses. The lowest incidence of the recurrence at

90 days was 52.1% in celivarone 50 mg compared with 67.1% in the placebo group ( $P = 0.055$ ); the corresponding values for symptomatic recurrence (the secondary endpoint) were 26.6 and 40.5%, respectively ( $P = 0.02$ ). No proarrhythmia or thyroid dysfunction was reported in this short-term study.

The double-blind placebo CORYFREE (COnTrolled Dose-Ranging studY of the eFFicacy and safEty of SSR149744C 300 or 600 mg for the Conversion of Atrial Fibrillation/flutter) trial has been completed, but the results have not yet been reported. The primary efficacy endpoint is the rate of conversion to sinus rhythm documented by ECG within 48 h after the first dose. The future of this agent is unknown.

### ATI-2042

There is on-going research into the development of amiodarone derivatives with modified binds within the molecule allowing rapid hydrolyzation, resulting in a more rapid action, a shorter half-life, and, possibly, a better risk-benefit ratio. There have been several amiodarone-based agents with a better safety profiles reported: aqueous amiodarone (*Amio-Aqueous*, Wyeth-Ayers), 'soft' amiodarone (ATI-2042, ARYx), and PM101 (Prism Pharmaceuticals). The development of aqueous amiodarone has recently been halted because of problems related to the solubility of the drug.

ATI-2042 is an oral, 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. Like amiodarone, ATI-2042 contains iodine, which is thought to contribute to the efficacy of amiodarone. In a pilot study in patients with paroxysmal AF, ATI-2042 reduced the amount of time the patients were in AF by up to 87%.<sup>29</sup> Atrial fibrillation burden was measured using electrograms stored in a dual-chamber pacemaker with significant storage capabilities. A phase II efficacy and safety study of ATI-2042 in patients with pacemaker is under way.

### PM101

PM101 is an amiodarone molecule combined with a cyclodextrin captisol (CyDex), which improves solubility of amiodarone in water, without the use of co-solvents (such as polysorbate 80 and benzyl alcohol). The advantages of PM101 include easy intravenous drug administration as a bolus, fast onset of action, and no necessity to dilute the drug compared with intravenous amiodarone. Phase I studies of the effects of PM101 on haemodynamics and heart rate in healthy volunteers have been completed ([clinicaltrials.gov/ct2/show/NCT00502346](http://clinicaltrials.gov/ct2/show/NCT00502346)).

## Selective $I_{Ks}$ blockers

To date, the anti-arrhythmic potential of  $I_{Ks}$  inhibition has not been vigorously assessed because of the lack of potent and selective  $I_{Ks}$  blockers. A chromanol derivative agent, HMR1556, is perhaps the only selective  $I_{Ks}$  blocker whose effects have been studied in atrial preparations and in animal models of AF. HMR1556 has ~1000-fold selectivity for  $I_{Ks}$  over  $I_{Kr}$ , but at higher concentration also inhibits  $I_{to}$ , the sustained outward current  $I_{sus}$ , and  $I_{CaL}$  currents. In a

canine model of vagal AF, HMR1556 prolonged the atrial effective refractory period and exerted a modest effect on the duration of induced AF only in the presence of intact  $\beta$ -adrenergic stimulation.<sup>30</sup> Intuitively, with rapidly receding interest to  $I_{Kr}$  blockers because of the modest efficacy and the significant proarrhythmic potential, the role of  $I_{Ks}$  inhibitors in pharmacological management of AF is not expected to be overwhelming. There is a significant concern that under certain conditions, such as type I long QT syndrome and in other circumstances where repolarization reserve is compromised,  $I_{Ks}$  blockade may be arrhythmogenic.

### Atrial repolarization-delaying agents

An attractive prospect in anti-arrhythmic drug therapy for AF is the introduction of agents with highly selective affinity to ion channels specifically involved in the repolarization processes in atrial tissue. The Kv1.5 channels carry the  $I_{Kur}$  current, which is a major determinant of action potential shape in atrial myocytes. Inhibition of the  $I_{Kur}$  current results in prolongation of the atrial effective refractory period. Because the Kv1.5 channel proteins are expressed predominantly in the atria,  $I_{Kur}$  blockers are expected to demonstrate atrial selectivity without affecting the electrophysiological properties of the ventricles. These investigational agents are also known as atrial repolarization-delaying agents (ARDAs) (Table 4). However, Kv1.5 channels are also present, though to a significantly lesser degree, in the ventricles and theoretically may prolong ventricular repolarization.<sup>31</sup> Unlike traditional  $I_{Kr}$  blockers, such as dofetilide and ibutilide, ARDAs may be more efficient in the remodelled atria and may therefore be more effective in converting AF.<sup>32,33</sup> Presently, there are several potential anti-arrhythmic drugs with an ARDA mode of action which are currently in clinical development. Many of these agents act upon more than one channel.

### Vernakalant

*Vernakalant* (RSD1235, Cardiome and Astellas) is in the most advanced phase of investigation and its intravenous formulation has recently been recommended for approval for pharmacological cardioversion of AF. Although  $I_{Kur}$  current is the main target of the drug, its mechanism of action involves blockade of several ion channels including  $I_{to}$ , and  $I_{Na}$ , but there is little impact on  $I_{Kr}$  or  $I_{Ks}$  ion currents. Therefore, vernakalant, although referred to as an ARDA, is a multi-channel blocker like many others of this type. Vernakalant slows conduction velocity within the atrium and prolongs its recovery. Because the  $I_{Na}$  blockade has fast offset kinetics, vernakalant is not likely to cause conduction disturbances and proarrhythmias at low heart rates. In a small, phase II, proof-of-efficacy study, 30 patients with AF duration under 72 h (mean duration 24 h) were randomized to a 10-min infusion of RSD1235 0.5 mg/kg followed by 1 mg/kg, or vernakalant 2 mg/kg followed by 3 mg/kg, or placebo.<sup>34</sup> Only the highest dose of vernakalant was effective in terminating AF in 61% of the patients within 80 min of exposure compared with a low dose (11%) and placebo (5%) efficacy. Recently, three medium-size randomized clinical studies and one open-label study of pharmacological cardioversion with vernakalant have been recently reported (Table 5).<sup>35–37</sup> Patients in the Atrial arrhythmia Conversion Trials (ACTs) I, III, and IV had AF lasting between 3 h and 45 days; patients in ACT II had AF lasting 3–72 h within 7 days after coronary bypass of valve replacement surgery. Arrhythmia conversion trial IV was an open-label study. Patients received a 10-min infusion of vernakalant 3 mg/kg or placebo (in ACT I, II, and III). If AF persisted after 15 min, a second infusion of 2 mg/kg was given. The primary endpoint was conversion to sinus rhythm within 90 min of dosing.

Vernakalant was significantly more effective than placebo in converting AF of more than 7 days. In ACT I and III, the

**Table 4** Reported atrial repolarization-delaying agents

Agent	Manufacturer	Mode of action	Route	Stage of development	Limitations
Vernakalant (RSD1235)	Cardiome and astellas	$I_{Kur}$ , $I_{to}$ , $I_{Na}$ , and $I_{Kr}$ blocker	IV and oral	Phase III studies completed; conditional FDA approval; oral formulation is in phase II	High conversion efficacy limited to AF < 72 h; moderately effective in AF of < 7 days; ineffective in atrial flutter
AZD7009 <sup>a</sup>	AstraZeneca	$I_{Na}$ , $I_{Kr}$ , $I_{Kur}$ , and $I_{to}$ blocker	IV	Reached phase II studies, now abandoned	Potent $I_{Kr}$ blockade, QT prolongation and torsades de pointes have been reported
AVE0118	sanofi aventis	$I_{Kur}$ , $I_{to}$ , and $I_{KACh}$ blocker	IV	Phase IIa studies have been conducted, further development not reported	Not reported; potential QT prolongation
S9947 and S20951	sanofi aventis	$I_{Kur}$ blocker; probably multiple-channel effects	IV	Experimental/phase I studies, not reported	Not reported; potential QT prolongation
NIP-141/142	Nissan Pharmaceuticals	$I_{Kur}$ , $I_{to}$ , $I_{KACh}$ , and $I_{CaL}$ blocker	IV	Experimental	Multiple-channel block; insufficient data
XEN-D0101/2	Xention	$I_{Kur}$ blocker	IV and oral	Entered phase II studies	Insufficient data

<sup>a</sup>More potent blocker of  $I_{Na}$  and  $I_{Kr}$  currents than the  $I_{Kur}$  current; AF, atrial fibrillation.

**Table 5** Summary of clinical studies of vernakalant in atrial fibrillation

Study	Number of patients	Phase	Patient characteristics	Dose of vernakalant	Placebo controlled	Primary endpoint	Outcome vs. placebo/control	Comments
CRAFT	56	II	AF 3–72 h	IV 0.5 + 1 mg/kg or IV 2 + 3 mg/kg	Yes	Conversion to SR during infusion or within 30 minutes after the last infusion	Converted to SR: 61 vs. 5%, $P < 0.001$ ; patients in SR at 30 min 56 vs. 5%, $P = 0.016$	Only higher dose of vernakalant was effective; median time to conversion 14 vs. 162 min (placebo)
ACT I	336 AF, 60 atrial flutter	III	AF 3 h–45 days (3 h–7 days, $n = 220$ ; 8–45 days, $n = 116$ )	IV 3 + 2 mg/kg	Yes	Conversion to SR within 90 minutes of drug initiation in AF 3 h–7 days	Converted to SR: 51.7 vs. 4%, $P < 0.001$	Highest conversion rates for AF $\leq 72$ h (78%); median time to conversion 11 min
ACT II	150	III	AF 3–72 h between 24 h and 7 days after cardiac surgery	IV 3 + 2 mg/kg	Yes	Conversion to SR within 90 minutes of drug initiation in AF 3 h–7 days	Converted to SR: 47 vs. 14%, $P < 0.001$	Median time to conversion 12 min
ACT III	262, 23 atrial flutter	III	AF 3 h–45 days (3 h–7 days, $n = 170$ ; 8–45 days, $n = 69$ )	IV 3 + 2 mg/kg	Yes	Conversion to SR within 90 minutes of drug initiation in AF 3 h–7 days	Converted to SR: 51.2 vs. 3.6%, $P < 0.001$	Highest conversion rates for AF $\leq 72$ h (71%); median time to conversion 8 min
ACT IV	167	IV, open label	AF 3 h–45 days (3 h–7 days, $n = 170$ ; 8–45 days, $n = 69$ )	IV 3 + 2 mg/kg	No	Conversion to SR within 90 min of drug initiation in AF 3 h–7 days	Converted to SR: 50.9%	Median time to conversion 14 min
Prevention	159	Ila	Persistent AF, post cardioversion	Oral 300 or 600 mg b.i.d.	Yes	SR at 1 month	Maintained SR at 1 month: 61 (each group) vs. 43% on placebo	The difference was significant for 300 mg b.i.d. ( $P = 0.048$ ), but not for 600 mg b.i.d. ( $P = 0.060$ )
Prevention and preliminary results	446	Ilb	Persistent AF, post cardioversion	Oral 150, 300, or 500 mg b.i.d.	Yes	SR at 3 months	Maintained SR at 3 months on 500 mg b.i.d.: 52 vs. 39%, $P < 0.05$	Median time to recurrence on 500 mg b.i.d. 90 vs. 39 days; no difference between lower doses and placebo

ACT, atria arrhythmia conversion trial; AF, atrial fibrillation; CRAFT, controlled randomized atrial fibrillation trial; IV, intravenous; SR, sinus rhythm.

conversion rates in the treatment arm were 51.7 and 51.2%, respectively, compared with 4 and 3.6% in the placebo arm.<sup>35,36</sup> In the open-label ACT IV study, the results were identical (50.9%) (presented at the Boston Atrial Fibrillation Symposium in January 2008). Vernakalant cardioverted 47% of the patients with post-operative AF enrolled in ACT II compared with 14% who converted spontaneously on placebo.<sup>37</sup> The median time to conversion was 11, 12, 8, and 14 min in ACT I to IV. The majority of patients (75–82%) converted after the first dose. The highest efficacy was observed for AF up to 72 h (70–80%) (Figure 3). However, the drug was relatively ineffective in patients with AF of more than 7 days and in atrial flutter, converting only 8 and 2.5% of the patients, respectively, in ACT I and 9 and 7%, respectively, in ACT III.

The drug was well tolerated, with no significant QTc prolongation or drug-related torsades de pointes. In the ACT I study, the QTc values after infusion were greater in the vernakalant group than in the placebo group and 24% of the patients in the vernakalant group had QTc >500 ms as opposed to 15% in the placebo group, but no torsades de pointes were reported during the first 24 h after infusion.<sup>35</sup> In three randomized studies, 39 (5.3%) of 737 patients treated with vernakalant developed any ventricular arrhythmia within 2 h after infusion and further 69 (9.4%) had an event between 2 and 24 h after infusion compared with 20 (6.3%) and 41 (13%) patients in the placebo arm. The most common (>5%) side effects of vernakalant were dysgeusia, sneezing, and nausea.<sup>38</sup>

The moderate overall anti-arrhythmic efficacy of vernakalant and particularly the absence of the anti-arrhythmic effect of  $I_{Kur}$  blockade in AF of more than 7 days may be explained by complex ionic remodelling during AF, including downregulation of  $I_{to}$ ,  $I_{Na}$ , and  $I_{CaL}$  currents. Blockade of  $I_{to}$  and  $I_{Na}$  by vernakalant may be more beneficial for prevention than conversion of AF. An oral formulation of vernakalant has been investigated in a phase IIa study.<sup>39</sup> Two doses of the drug (300 and 600 mg twice daily) were compared with placebo. The follow-up period was limited

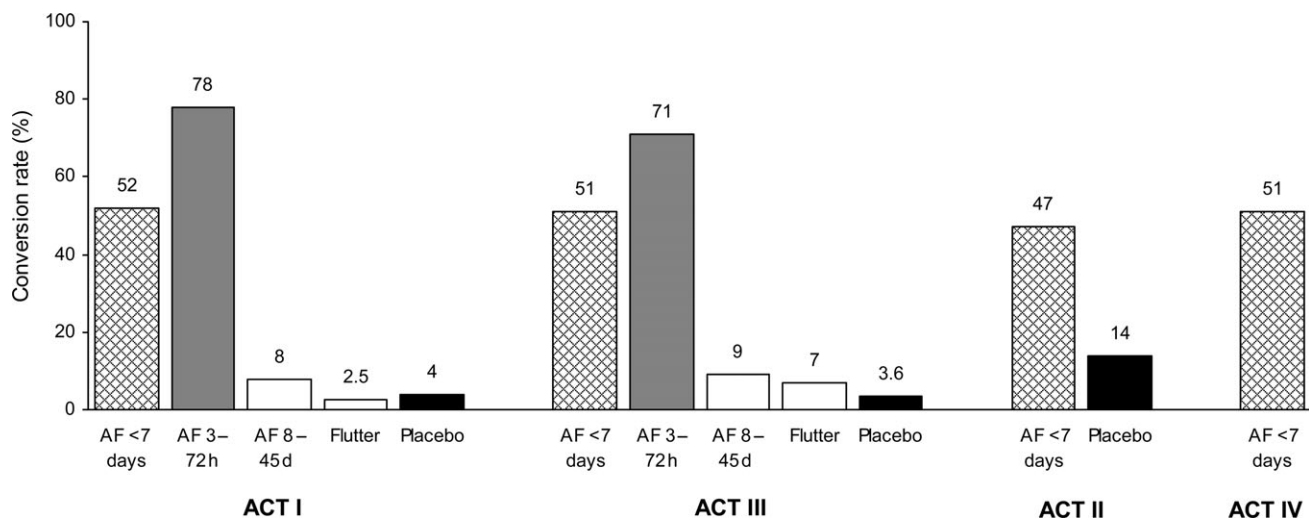
to 28 days because of available toxicology data and because the efficacy of anti-arrhythmic agents in the early post-cardioversion period is of particular interest. Both doses of the drug equally suppressed arrhythmia recurrence (in both groups, 61% of the patients treated with vernakalant were in sinus rhythm at the end of the study), although the reduction of arrhythmia recurrence rates was statistically significant only with 300 mg ( $P < 0.048$ ). When the two groups were combined, vernakalant was significantly superior to placebo ( $P = 0.028$ ). No drug-related torsades de pointes were reported. However, the study result did not allow an ideal dose of the drug to be decided with any certainty.

The preliminary results of a phase IIb randomized, double-blind study of three doses of vernakalant (150, 300, or 500 mg twice daily) in 446 patients after pharmacological (vernakalant) or electrical cardioversion were released to the public domain in March 2008.<sup>40</sup> Patients treated with the highest dose were more likely to maintain sinus rhythm at 3 months compared with placebo (52 vs. 39%,  $P < 0.05$ ); the median time to recurrence of AF was greater than 90 days in the vernakalant 500 mg group compared with 39 days in the placebo group. There was no statistical difference between vernakalant 150 and 300 mg twice daily and placebo. The safety data from the interim analysis also suggest that vernakalant was well-tolerated. There were no reports of torsade de pointes or drug-related deaths. Phase III studies of oral vernakalant are presently planned.

## Other atrial repolarization-delaying agents

### XEN-D0101

XEN-D0101 (Xention) is highly selective for the Kv1.5 channels over non-target ion channels. In dogs with acute and chronic AF induced by rapid atrial pacing, XEN-D0101 selectively prolonged the atrial effective refractory period and decreased the duration of AF.<sup>41,42</sup> The drug is available in both intravenous and oral formulations. Clinical studies



**Figure 3** Percentage of patients with atrial fibrillation that converted to sinus rhythm within 90 min after the start of infusion of vernakalant in the Atrial arrhythmia Conversion Trials (ACTs) I to IV. ACTs I, II, and III were randomized, double-blind, placebo-controlled studies; ACT IV was an open-label study. ACTs I, III, and IV enrolled patients with atrial fibrillation or flutter of 3 h to 45 days; ACT II enrolled patients with atrial fibrillation 24 h to 7 days after heart surgery. Vernakalant was significantly more effective than placebo ( $P \leq 0.0001$ ). AF, atrial fibrillation.

with this compound to maintain sinus rhythm after cardioversion in patients with persistent AF are under way.

However, the potential efficacy of highly selective  $I_{Kur}$ -blocking agents has yet to be demonstrated. There are concerns that isolated  $I_{Kur}$  blockade may not be sufficient for the prolongation of the atrial effective refractory period because the  $I_{Kur}$  current is responsible predominantly for the early repolarization phase 1 and contributes less to the plateau phase 2. Furthermore,  $I_{Kur}$  block may move the plateau to a more positive potential which in turn may activate the  $I_{Kr}$  current and accelerate phase 3 late repolarization, thus abbreviating the action potential.

#### AVE0118

*AVE0118* (sanofi aventis) blocks the  $I_{Kur}$  and several other currents such as  $I_{to}$  and the acetylcholine-activated potassium current ( $I_{KACH}$ ). Animal studies have demonstrated the ability of *AVE0118* to prolong the atrial effective refractory period and cardiovert AF in a goat model with little effect on ventricular refractoriness and the QT interval.<sup>33</sup> Restoration of sinus rhythm with *AVE0118* was associated with improvement in atrial contractility, whereas conventional positive inotropic drugs (dobutamine, digoxin) and calcium sensitizers had no effect on the atrial function after cardioversion.<sup>43</sup> The greatest effect on atrial refractoriness appeared to be confined to the left atrium and was less pronounced in the right atrium. In normal goat atria, both *AVE0118* and dofetilide showed a clear rate dependency of their effects on atrial refractoriness; however, in remodelled atria after 48 h of continuous AF, *AVE0118* prolonged the atrial effective refractory period to a pre-remodelled level and prevented induction of AF in two-thirds of experiments, whereas dofetilide lost its effects on atrial refractoriness and vulnerability.<sup>33</sup> No clinical studies with *AVE0118* have been reported and its development has probably been terminated.

#### AZD7009

*AZD7009* (AstraZeneca) was initially classified as an ARDA class drug, but later was found to block multiple repolarizing potassium channels including  $I_{Kur}$ ,  $I_{to}$ ,  $I_{Kr}$ , and the  $I_{Ks}$  currents as well as the late sodium depolarizing current ( $I_{Na}$ ).  $I_{Kr}$  block occurs at lower concentrations than those required for  $I_{Kur}$  and  $I_{to}$  blockade and may therefore increase the potential of the drug to prolong the action potential in the ventricles and cause torsades de pointes. Early animal studies have suggested that the effects of *AZD7009* are more evident in the atria and are minimal in the ventricles.<sup>44</sup> Furthermore, the drug has the ability to prolong the ventricular action potential homogeneously in all cell layers (epi-, endo-, and mid-myocardium), without increasing transmural dispersion of repolarization. Blockade of the late  $I_{Na}$  current may counteract an excessive repolarization delay in M-cells and Purkinje fibres. Animal studies have demonstrated the ability of *AZD7009* to increase atrial refractoriness, suppress AF inducibility, and rapidly convert AF, particularly in volume-overload atria.<sup>45</sup>

In a dose-ranging clinical study in 122 patients with AF or atrial flutter of 2–90 days duration, *AZD7009* restored sinus rhythm in a dose-dependent manner in 45–58% of the patients within 1 h after the start of infusion.<sup>46</sup> No spontaneous conversion occurred in the placebo arm. The conversion rates were higher in patients with the arrhythmia

<1 week (78%) and in patients with AF and no history of atrial flutter (70%). Pre-treatment with *AZD7009* increased the success rate of electrical cardioversion and reduced the occurrence of immediate recurrence of AF. However, the development of *AZD7009* was stopped because of its extra-cardiac side effects and the potential to significantly prolong the QT interval. Bradycardia-related QTc >550 ms (Fridericia) was seen in four patients after 1 h and seven patients after 3 h of infusion. Although no episodes of torsades de pointes were reported, non-sustained polymorphic ventricular tachycardia with torsade-de-pointes-like features was detected in one patient during 24-h monitoring.

#### NIP-141/142

*NIP-141/142* (Nissan Pharmaceuticals) are multi-channel blockers with a high affinity to K1.5 channels, but it also affects  $I_{to}$ ,  $I_{KACH}$ , and  $I_{CaL}$  currents. The ability of these agents to prolong the atrial effective refractory period, to prevent AF induction by vagal stimulation, and to suppress focal activity induced by aconitine has been demonstrated in animals.<sup>47,48</sup> The drug has not been studied in the clinical setting.

### Sodium current blockers

#### Pilsicainide

Pilsicainide (Sunrhythm, Suntory Ltd) is a class I anti-arrhythmic agent without the negative inotropic effect. Pilsicainide demonstrated a modest efficacy in converting AF to sinus rhythm, with a conversion rate of 45% within 90 min in patients with recent-onset AF compared with 8.6% on placebo and was ineffective in AF of longer duration.<sup>49</sup> The drug showed no superiority to other members of its class (IC) in maintaining sinus rhythm in the long-term and it exhibited a similar adverse event profile to other class IC agents.

#### Ranolazine

Fast atrial rates during AF lead to ischaemia and oxidative injury of the atrial myocardium. During ischaemia, there is an increase in the late phase of the inward sodium current (late  $I_{Na}$ ), which raises the intracellular concentration of sodium. Increased intracellular sodium stimulates the  $Na^+/Ca^{2+}$  exchanger and causes it to operate in a 'reverse' mode bringing calcium into the cell. The augmented late  $I_{Na}$  current causes heterogeneity of depolarization and promotes re-entrant arrhythmias. Ranolazine is an anti-anginal agent which also blocks several ion channels and exchangers, predominantly the late but also the peak  $I_{Na}$ ,  $Na^+/Ca^{2+}$  exchanger,  $I_{CaL}$  the late calcium current, and  $I_{Kr}$  and  $I_{Ks}$  currents.<sup>50</sup> Ranolazine is a strong inhibitor of the late  $I_{Na}$  current with a potency of 6  $\mu$ mol/L (50% inhibition), which is ~38-fold greater than that required for the inhibition of the peak  $I_{Na}$  current. By preferentially inhibiting the late  $I_{Na}$  current, ranolazine has been shown in isolated hearts and animal models to reduce intracellular sodium and calcium overload caused by ischaemia and to suppress early afterdepolarizations.

The potential anti-arrhythmic effects of ranolazine has been evaluated as part of the safety analysis in the MERLIN-TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST-elevation acute coronary syndrome—

Thrombolysis in Myocardial Infarction 36) trial.<sup>51</sup> In this study, 6560 patients hospitalized with acute coronary syndromes were randomized to ranolazine or placebo in addition to standard medical therapy. A continuous ECG Holter recording was performed for the first 7 days after randomization to assess for arrhythmias as part of a safety analysis. Therapy with ranolazine resulted in a significantly lower incidence of tachyarrhythmias compared with placebo, particularly non-sustained ventricular tachycardia.

At therapeutic concentrations (2–6  $\mu\text{mol/L}$ ), ranolazine also affects  $I_{Kr}$  (50% inhibition at 12  $\mu\text{mol/L}$ ) and can potentially prolong the action potential, but this effect is offset by more potent late  $I_{Na}$  blockade. The net effect and clinical consequence of multiple channel blockade by ranolazine is a modest increase in the mean QT interval by 2–6 ms.<sup>51</sup> In isolated canine ventricular myocytes and wedge preparations, ranolazine prolonged the action potential duration of the epicardial layer due to the predominant  $I_{Kr}$ -blocking effects, but shortened the action potential duration of M cells due to predominant  $I_{Na}$  blockade and reduced another proarrhythmic substrate—transmural dispersion of repolarization.<sup>50</sup> Recent experiments in canine-isolated perfused atrial and ventricular preparations have suggested that sodium channel characteristics may differ between atrial and ventricular cells and that ranolazine has shown greater affinity to sodium channels in the atria than in the ventricles.<sup>52</sup> The potential of ranolazine at clinically relevant concentrations of 5–10  $\mu\text{mol/L}$  to prevent induction of and to terminate AF was demonstrated in isolated arterially perfused canine right atria during acetylcholine infusion and during ischaemia.<sup>52</sup> A phase III study in patients with AF is planned. Because the therapeutic dose is established, there will probably be no need in dose-ranging phase II studies.

### Agents with novel mechanisms of action

Novel mechanisms of action are now being sought (Figure 1). Experimental anti-arrhythmic agents targeting specific pathophysiological mechanisms of AF are in development, including agents that are capable of reversing ion channel remodelling, and yet others which regulate intracellular calcium homeostasis and cell-to-cell coupling.<sup>10</sup>

#### Atrial acetylcholine-regulated potassium current ( $I_{KACh}$ ) inhibitors

It is generally accepted that vagal nerve activation contributes to initiation of AF. Acetylcholine stimulates muscarinic M-receptors and activates the  $I_{KACh}$  current in the atria, which is carried by Kir3.1/3.4 channels and normally is small or absent. Increased activity of inward  $I_{KACh}$  causes shortening of the atrial action potential and thus promotes AF. However, the precise mechanism by which the  $I_{KACh}$  current mediates the shortening of the action potential in response to M-receptor stimulation is unknown. One possibility is that  $I_{KACh}$  contributes to higher background inward rectifier current ( $I_{K1}$ ) by developing agonist-independent spontaneous activity.<sup>53</sup> An increase in  $I_{K1}$  results in shortening of the atrial potential and hyperpolarization of the resting membrane potential. Subsequently, the  $I_{Na}$  current is increased and atrial excitability is enhanced. Recent studies have shown that ionic remodelling induced by

rapid atrial pacing and induction of AF also results in increased constitutively active  $I_{KACh}$  by enhancing spontaneous channel opening, even in the absence of acetylcholine.<sup>54</sup> In tachycardia-remodelled dog atria, tertiapin-Q, a highly selective blocker of Kir3 channels, decreased the  $I_{KACh}$ , prolonged the action potential to a greater extent than in intact atria, and impeded induction of AF.<sup>55</sup> Thus, blockade of  $I_{KACh}$  may potentially be anti-arrhythmic and, because  $I_{KACh}$  is absent in the ventricles, its anti-arrhythmic effect will be specific to the atria.

Some anti-arrhythmic agents, such as amiodarone, flecainide, and ibutilide, exhibit  $I_{KACh}$ -blocking properties. KB130015 is an amiodarone derivative which is also a potent  $I_{KACh}$  inhibitor. Using the whole-cell voltage-clamp technique in isolated guinea pig myocytes, KB130015 prevented vagally induced AF by the direct effect on the extracellular but not intracellular part of the  $I_{KACh}$  channel.<sup>56</sup> NIP-151 is another potent inhibitor of the  $I_{KACh}$  current with lesser effects on other channels, which has been shown to selectively prolong the atrial effective refractory period and terminate AF in canine models.<sup>57</sup>

Preliminary reports on two competitive inhibitors of acetylcholine at the neuromuscular junction, cisatracurium, and mivacurium have suggested that these agents are effective in preventing triggered firing and re-entrant AF in anesthetized dogs during right vagus nerve stimulation, without facilitating atrioventricular conduction or producing sinus tachycardia, and may represent a new class of atrial-specific anti-arrhythmic agents.<sup>58</sup> Agents with the effect on the  $I_{KACh}$  current remain experimental. It is unknown whether anticholinergic effects of  $I_{KACh}$  blockers on smooth muscle cells and the vagal component of the sinus node regulation may be an obstacle in the development of these agents.

### Agents targeting abnormal calcium handling

Increased intracellular calcium ( $\text{Ca}^{2+}$ ) concentrations and abnormalities in  $\text{Ca}^{2+}$  handling have been linked to initiation of AF by promoting delayed and late phase III early afterdepolarizations sufficient to initiate ectopic activation.<sup>59,60</sup> Agents that block L-type (e.g. verapamil) or T-type (e.g. mibefradil)  $\text{Ca}^{2+}$  channels have been shown to have the potential to suppress fibrillatory activity in the atria by reducing  $\text{Ca}^{2+}$ .<sup>61,62</sup> Release of  $\text{Ca}^{2+}$  from sarcoplasmic reticulum via specialized channels, known as ryanodine receptors (RyR2 in the heart) because of their initial identification via high-affinity binding of the toxin ryanodine, is regulated by intracellular  $\text{Ca}^{2+}$  concentration. A small increase in intracellular  $\text{Ca}^{2+}$  produced by the  $I_{CaL}$  current during cell depolarization stimulates opening of RyR2 and release of a much greater amount of  $\text{Ca}^{2+}$  from intracellular stores ( $\text{Ca}^{2+}$  spark).<sup>63</sup> If the sarcoplasmic reticulum is overloaded with  $\text{Ca}^{2+}$ , the release can occur in the absence of the  $I_{CaL}$  current. Abnormality in the RyR2 macromolecular complex structure or regulatory proteins and enzymes [e.g. calstabin 2 and  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II (CAMKII)] may change the open and close state of RyR2 channels and cause  $\text{Ca}^{2+}$  leak, leading to depletion of sarcoplasmic reticulum  $\text{Ca}^{2+}$  stores required for excitation-contraction and increasing the probability of afterdepolarizations.

Calstabin 2, or FK-binding protein FKBP12.6 (initially identified by binding the immunosuppressant FK506, hence

the name), binds to RyR2 and decreases its open probability.<sup>63</sup> Increased protein kinase A phosphorylation of RyR2 which occurs, for example in heart failure, attenuates calstabin binding, and increase  $\text{Ca}^{2+}$  leak during diastole. Recently, alterations in regulation and function of the RyR2 macromolecular complex resulting in protein kinase A hyperphosphorylation of RyR2 and partial depletion of calstabin 2 have been found in a canine model of AF induced by rapid right atrial pacing and in human atrial tissue from patients with AF and normal left ventricular function.<sup>64</sup> Conversely, agents that boost calstabin binding may reduce  $\text{Ca}^{2+}$  leak and may have an anti-arrhythmic effect.  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II phosphorylates and activates RyR2 and increases the  $I_{\text{CaL}}$  current;<sup>63</sup> therefore, inhibition of CAMKII may also have an anti-arrhythmic potential. Consequently, an experimental CAMKII inhibitor, KN-3, prevented induction of triggered activity by isoproterenol and phenylephrine in the rabbit pulmonary veins.<sup>65</sup>

### JTV519

JTV519 (K201, Japan Tobacco, Aetas Pharma) acts by enhancing the binding affinity of calstabin 2 for RyR2 and preventing the dissociation of calstabin 2 from RyR2. It stabilizes the channel in the closed state, thus reducing  $\text{Ca}^{2+}$  leak.<sup>64</sup> JTV-519 has been shown to suppress the inducibility of sustained AF and shortened the duration of induced atrial flutter in a canine sterile pericarditis model and to prevent delayed depolarizations and reduce the firing rate in isolated rabbit pulmonary vein myocytes.<sup>66,67</sup>

### $\text{Na}^+/\text{Ca}^{2+}$ exchanger inhibitors

Uptake of  $\text{Ca}^{2+}$  occurs via a sarcoplasmic endoplasmic reticulum adenylate-triphosphate (ATP) dependent  $\text{Ca}^{2+}$ -ATPase (SERCA), which is inhibited by phospholamban and a sarcolemmal transporter,  $\text{Na}^+/\text{Ca}^{2+}$  exchanger.<sup>63</sup> The  $\text{Na}^+/\text{Ca}^{2+}$  exchanger exchanges one intracellular  $\text{Ca}^{2+}$  ion accumulated in the cell during the action potential for three extracellular sodium ions. During fast atrial rates caused by AF or induced by pacing, a larger increase in intracellular sodium relative to calcium may cause the bidirectional exchanger to work in the reverse mode, bringing calcium into the cell, thus contributing to the shortening of the action potential.

KB-R7943 (Kanebo) preferentially inhibits the reverse mode of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger. The underlying molecular mechanism for this directional specificity is not clear, but KB-R7943 appears to block calcium influx irrespective of the presence or absence of extracellular calcium. In anaesthetized dogs, KB-R7943 attenuated shortening of the atrial effective refractory period caused by pacing-induced AF.<sup>68</sup> The drug also blocks multiple channels, including those which carry  $I_{\text{to}}$ ,  $I_{\text{K}}$ ,  $I_{\text{K1}}$ ,  $I_{\text{Na}}$ , and  $I_{\text{CaL}}$  currents, and has been found to prolong the ventricular effective refractory periods.<sup>69</sup> Another exemplary drug that prevents sodium and calcium overload is SEA0400 (Taisho Pharmaceutical) which is more selective and potent than KB-R7943.<sup>70</sup>

**Stretch receptor antagonists.** Experiments have suggested that atrial dilatation may produce electrophysiological effects on the atria by the mechanism of mechano-electrical feedback which involves stretch-activated channels.<sup>71</sup> These include non-specific channels permanent to  $\text{Ca}^{2+}$ , sodium, and potassium ions and channels which are selective to potassium or chloride ions and act as mediators converting mechanical gradients caused by

stress to electrical gradients resulting in increased automaticity. Atrial stretch causes the atrial refractory period to shorten and conduction to slow, which provides a substrate for functional re-entry. Stretch is also involved in structural remodelling by inducing fibrosis and producing anisotropic conduction. Therefore, blockade of stretch-activated channels may represent a novel anti-arrhythmic approach to AF, particularly in the presence of elevated atrial pressure or volume. Gadolinium, a non-specific stretch-activated channel blocker, prevented induction of AF and suppressed the occurrence of spontaneous AF during increased atrial pressures in isolated rabbit hearts, whereas in the absence of gadolinium, AF could be induced in each preparation.<sup>72</sup>

Gadolinium and other non-selective blockers, such as amiloride, and some cationic antibiotics cannot be applied under physiological conditions. GsMTx-4, a 35-aminoacid peptide toxin, which was isolated from the venom of the Chilean Rose tarantula *Grammostola spatulata* in 2000, is a selective and potent blocker of cationic stretch-activated channels. It has two enantiomers, with the D-enantiomer being more resistant to hydrolysis by endogenous proteases. GsMTx-4 has been shown to prevent inducibility of AF in the rabbit atria without any measurable effect on the duration and shape of the atrial action potential.<sup>73</sup> In the presence of GsMTx-4, induction of AF was possible only at significantly higher atrial pressures compared with control preparations ( $18.5 \pm 0.5$  vs.  $8.8 \pm 0.2$  cm H<sub>2</sub>O). However, GsMTx-4 does not possess atrial selectivity and produces similar effects on the ventricular myocardium.

Activation of stretch-activated channels depends on membrane fluidity, which can be modified by PUFAs. PUFAs incorporated in cell membranes increase membrane fluidity and may reduce stretch-mediated electrophysiological effects. Experiments on isolated Langedorff-perfused hearts from rabbits fed with PUFA-rich diet have demonstrated an increased resistance to stretch-mediated changes in atrial electrophysiological properties.<sup>74</sup> In the treated group, a greater stretch was required to produce similar abbreviations of atrial refractoriness which were observed in control animals at lower stretch levels. The high PUFA content in membranes of atrial myocytes was associated with less inducible and less sustainable AF. In rat atrial myocytes, PUFAs added as free acids significantly reduced the level of asynchrony and terminated asynchronous contractile activity induced by isoproterenol, the effect mediated by the increased fluidity of cell membranes.<sup>75</sup> Although the anti-arrhythmic potential of PUFAs has been demonstrated in specific forms of AF (e.g. after cardiac surgery), data provided by epidemiological studies are highly controversial.<sup>12</sup>

### Gap junction modifiers

Remodelling of electrophysiological and structural properties of the fibrillating atria involves changes in junctions forming the atrial intercalated disc: fascia adherens, the desmosomes, and gap junctions and their proteins (N-cadherin, desmoplakin, and connexins).<sup>76</sup> Gap junctions are specialized membrane regions which directly connect the cytoplasmic compartments of two adjacent cells and enable intercellular communication. Cardiac gap junction channels constitute the basis for the electrical syncytial

properties of the heart and propagation of the action potential. The gap junction channel is formed by two connexons which are located on adjacent myocytes and consist of six proteins (connexins). Two major isoforms of connexins with a molecular weight of 40 and 43 kDa are specific for the cardiac tissue, with connexin 40 predominantly expressed in the atrial myocardium and the conduction system. In addition, connexin 45 is found in conduction tissue. Increased dephosphorylation of connexins secondary to inhibition of protein kinases, activation of phosphatases, or a loss of ATP increases the turnover of connexins and causes functional changes of connexin proteins.

Remodelling of gap junctions associated with a decrease in the expression and/or redistribution of connexins leads to impaired intercellular communication and reduced conductance between cardiomyocytes.<sup>77</sup> There is evidence that links connexin 40 polymorphism (specifically, lack of connexin 40) to enhanced atrial vulnerability and increased risk of AF.<sup>78</sup> Local angiotensin II can modify gap junction properties and losartan has been shown to prevent worsening of cell communication in cardiomyopathy.<sup>79</sup> This effect is mediated by an increase in gap junctional conductance and by the reduction of interstitial fibrosis. Among traditional anti-arrhythmic drugs, only tedisamil has been reported to enhance gap junctional conductance at early stages of cardiomyopathy in hamsters, by activating adenylcyclase and consequent phosphorylation of connexins.<sup>80</sup> This prompted interest in agents that specifically increase gap junction conductance via activation of protein kinase C and enhanced phosphorylation of connexins.

### Anti-arrhythmic peptide

The first specific gap junction modulator, called an anti-arrhythmic peptide (AAP10), was isolated from the bovine atria in 1980 and had a molecular weight of 470 kDa.<sup>81</sup> A

synthetic anti-arrhythmic peptide (AAP10) was synthesized in 1994 and has been shown to improve the connexin function by protein kinase C-mediated phosphorylation, but was too unstable to be used in clinical practice.<sup>82</sup>

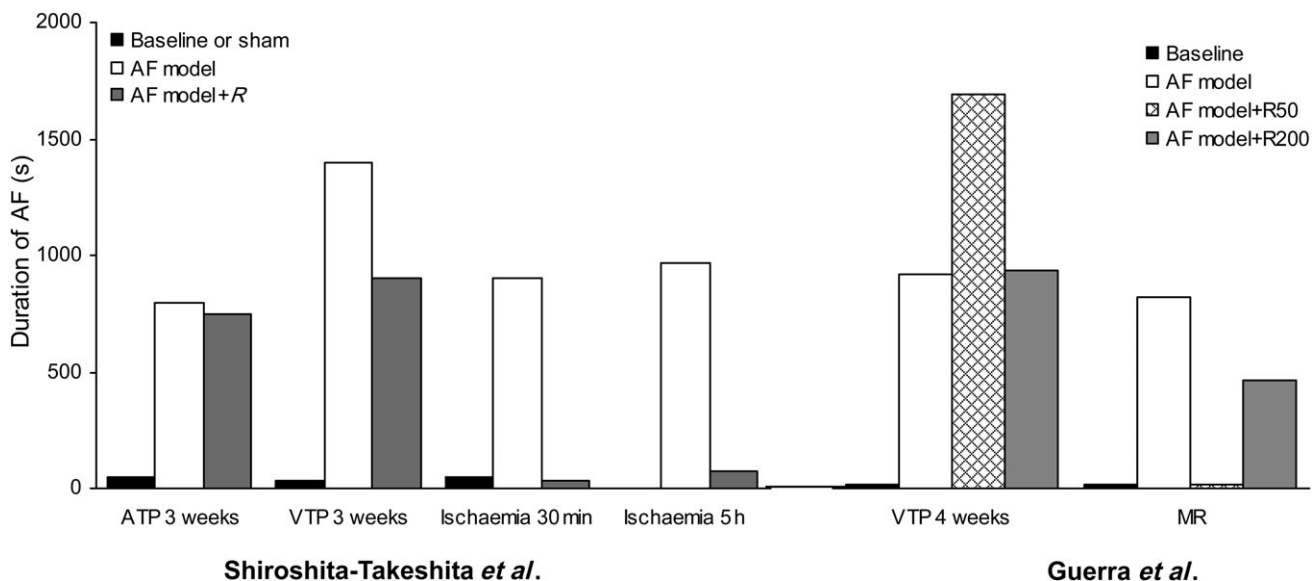
### Rotigaptide

A hexapeptide, *rotigaptide* (GAP-486, ZP123, Zealand Pharma/Wyeth), was developed on the basis of the original AAP structure with D-isomers substituted for L-isomers and is now under investigation. Rotigaptide has been shown to prevent metabolic stress-induced decrease in atrial conduction in isolated left atrial tissue in rats, but had no effect on gap junction conduction under physiological conditions.<sup>83</sup> In dog models of acute myocardial ischaemia and mitral insufficiency, rotigaptide prevented induction of AF by preventing slowing of conduction, but had no effect on AF promotion in dogs subjected to atrial or ventricular tachypacing (Figure 4).<sup>84,85</sup> Rotigaptide had no effect on the atrial effective refractory period.

### GAP-134

Zealand Pharma and Wyeth also reported on GAP-134, a dipeptide gap junction modifier which was developed specifically for therapy of AF.<sup>86</sup> GAP-134 prevented slowing of the conduction velocity in rat atrial preparations exposed to metabolic stress and suppressed induction of AF in a canine sterile pericarditis model.<sup>86</sup>

Although gap junction modifiers have the potential to prevent AF inducibility in acute and sub-acute settings, it is unclear whether they are equally effective in chronically remodelled atria. There are chamber-related differences in connexin expression in the normal human heart, including atria.<sup>87</sup> Experimental observations in animal models of AF<sup>88,89</sup> and the results of studies in the human right and left atrial tissue<sup>89-93</sup> demonstrated the whole range of



**Figure 4** Duration of induced atrial fibrillation before and after rotigaptide in different dog models of atrial fibrillation. Mean plasma concentrations of rotigaptide in the study of Shiroshita-Takeshita *et al.*<sup>85</sup> was 132–179 nmol/L; mean plasma concentrations of rotigaptide in the study by Guerra *et al.*<sup>84</sup> were 56 nmol/L (R50) or 181 nmol/L (R200). Note that rotigaptide at lower concentrations (a target of 50 nmol/L) was more effective than at higher concentrations (a target of 200 nmol/L) in reducing the duration of atrial fibrillation in the mitral regurgitation model. ATP, atrial tachypacing; MR, mitral regurgitation; R, rotigaptide; R50, rotigaptide at 50 nmol/L; R200, rotigaptide 200 nmol/L; VTP, ventricular tachypacing.

**Table 6** Evidence of connexin remodelling in atrial fibrillation in humans

Study	Polontchouk <i>et al.</i> <sup>89</sup>	Dupont <i>et al.</i> <sup>90</sup>	Kostin <i>et al.</i> <sup>92</sup>	Nao <i>et al.</i> <sup>91</sup>	Wetzel <i>et al.</i> <sup>93</sup>
Number	12 AF, 12 SR	9 AF, 10 SR	31 AF, 22 SR	10 AF, 20 SR	77 AF, 15 SR
Heart disease	Mixed	CABG	Mixed	20 MV disease and 10 CABG	41 lone AF, 36 MV disease
AF duration	Permanent	New AF post-CABG	Permanent	Permanent	28 paroxysmal, 49 permanent
Tissue sample	RAA	RAA	RAA and RAFW	RAA	LAA
Connexin 40	Increased by 2.3-fold	Insignificantly increased, redistributed	Reduced by two-fold in RAA, but increased in RAFW	Reduced by 2.5-fold, but phosphorylated Cx40 increased by two-fold	Significantly increased in all AF
Connexin 43	Re-distribution to lateral cell-cell contacts	No difference between AF and SR groups	Reduced by two-fold, re-distributed to lateral cell-cell contacts	No differences between AF and SR groups	Increased in AF with MV disease (n.s.)

AF, atrial fibrillation; CABG, coronary artery by-pass grafting; LAA, left atrial appendage; MV, mitral valve; RAA, right atrial appendage; RAFW, right atrial free wall; SR, sinus rhythm.

changes from connexins being overexpressed, reduced, or simply re-distributed, with increased amount of protein accumulated in the sites of lateral contacts between myocytes (Table 6). The electrophysiological effects of gap junction modifiers, in situations when connexins are re-distributed but their expression and function remain unaltered, have not been explored. Furthermore, there are potential concerns about the safety of gap junction modifiers because theoretically, pharmacological restoration of intercellular coupling may destabilize re-entry and be proarrhythmic.

### Agents targeting ischaemia-related arrhythmogenic mechanisms

Experimental agents that regulate channels and proteins that operate during myocardial ischaemia, such as selective  $K_{ATP}$ -channel blockers and  $Na^+/H^+$  exchanger inhibitors, are potentially promising for the prevention of AF from becoming sustained. Increased  $Na^+/H^+$  exchanger activity during intracellular acidosis caused by myocardial ischaemia leads to sodium overload and causes the  $Na^+/Ca^{2+}$  exchanger to work in a reverse mode (i.e. bringing  $Ca^{2+}$  ions into the cell), resulting in  $Ca^{2+}$  overload and shortening of the action potential.<sup>94</sup> Further shortening of the action potential may occur due to ischaemia-induced loss of potassium ions via the sarcolemmal ATP-sensitive ( $K_{ATP}$ ) channels which open during myocardial ischaemia<sup>93</sup> and are responsible for ischaemia-induced potassium ion loss and shortening of the action potential. A number of  $Na^+/H^+$  exchanger inhibitors (e.g. *cariporide*, sanofi aventis, *eniporide*, Merck, *sabiporide*, Boehringer Ingelheim, and *zoniporide*, Pfizer) and selective  $K_{ATP}$ -channel blockers (*clamilant* and *HMR 1883*, sanofi-aventis) have been investigated in models with acute ischaemia. In a canine model of AF induced by atrial tachypacing in the presence of right coronary artery ligation,  $Na^+/H^+$  exchanger inhibition has been shown to prevent the reduction of AF vulnerability and attenuate changes in the left atrial function.<sup>95,96</sup> However, these results have not been reproduced in experiments in goats.<sup>97</sup> There are no data on the use of these agents in AF in man.

### 5-Hydroxytryptamine-4 receptor antagonists

Serotonin 5-hydroxytryptamine-4 (5-HT<sub>4</sub>) receptors are present in the atria and enhance the  $I_{Ca,L}$  current via a cyclic adenosine monophosphate-dependent protein kinase.<sup>98</sup> Consequently, the  $I_{Kr}$  is augmented via a calmodulin-dependent pathway. A 5-HT<sub>4</sub> inhibitor *RS-100302* (Roche) was highly effective in suppressing AF in anesthetized pigs,<sup>99</sup> but clinical studies with *piboserod* (GlaxoSmithKline) showed no efficacy in preventing AF recurrence after cardioversion.

### Drugs targeting atrial fibrillation substrate

#### Renin-angiotensin system inhibitors

Atrial stretch associated with AF increases local synthesis of angiotensin II and initiates a cascade of phosphorylation processes that activate a family of mitogen-activated protein kinases. The density of angiotensin II receptors in the atria is generally greater than in the ventricles, making the atria more vulnerable to the effects of angiotensin II. Mitogen-activated protein kinases promote atrial myocyte hypertrophy, fibroblast proliferation, accumulation of collagen, and apoptosis. Atrial interstitial fibrosis can lead to non-uniform anisotropy in conduction. In addition, angiotensin II modifies atrial electrophysiology by indirect effects on ion channels, increases  $Ca^{2+}$  influx, promotes inflammation, and may also impair cell-to-cell coupling associated with gap junctional remodelling.<sup>100</sup> There is accumulating evidence that, beyond its therapeutic effects on underlying heart disease, such as hypertension and heart failure, inhibition of the renin-angiotensin-aldosterone system may offer some protection against atrial structural and possibly electrical remodelling associated with AF.<sup>11</sup>

#### Pirfenidone

*Pirfenidone* (InterMune) is a newly developed anti-fibrotic agent which inhibits collagen synthesis, downregulates production of pro-fibrotic cytokines, and blocks cytokine-induced fibroblast proliferation. Pirfenidone has demonstrated activity in multiple fibrotic conditions,

including renal, liver, and pulmonary fibrosis. The anti-arrhythmic potential of pirfenidone has recently been shown in a canine model of heart failure induced by rapid ventricular pacing. Pirfenidone administered orally for 3 weeks attenuated left atrial fibrosis which translated into a variety of beneficial electrophysiological effects: prolongation of the atrial effective refractory period, an increase in wavelength, a decrease in dispersion of repolarization, and a reduction in the conduction heterogeneity index, and an overall decrease in AF vulnerability.<sup>101</sup> Pirfenidone reduced the amount of mitogen-activated protein kinases which mediate the effects of angiotensin II at the tissue level and also modified the expression of matrix-degrading enzymes—metalloproteinases (MMP) and their endogenous inhibitors.<sup>101</sup> An imbalance between expression of MMP and their tissue inhibitors plays an important role in extracellular matrix remodelling associated with AF. An increase in MMP activity can induce matrix degradation and lead to dilatation, whereas a decrease can reduce the extracellular matrix breakdown and lead to fibrosis.<sup>12</sup> The expression of MMP-1, MMP-2, and MMP-9 correlated with the degree of fibrosis and dilatation in the left and right human atrial tissue samples.

The role of statins which target specific AF mechanisms, such as inflammation, oxidative injury, and extracellular matrix remodelling, is under investigation.<sup>12</sup> Metabolic modulation of altered atrial myocyte energetics with agents such as trimetazidine or perhexilene has theoretical advantages as a potential novel therapeutic strategy.

## New drugs for rate control

In contrast to drugs for cardioversion, rate control agents have seen little advances and are limited to  $\beta$ -blockers, calcium-channel blockers, digoxin, and adenosine.

### Adenosine A<sub>1</sub> receptor agonists

#### Tecadenoson

*Tecadenoson* (CVT-510, CV Therapeutics) is an adenosine derivative with a high specificity to A<sub>1</sub> receptors and a potency to prolong atrioventricular node conduction at doses that do not reduce blood pressure or cause bronchospasm by stimulation of A<sub>2</sub> receptors. It has no effect on ventricular conduction and very little effect on atrial action potential duration. Its half-life is ~30 min. Because of the selective A<sub>1</sub> receptor properties, tecadenoson may prove to be a potent and safe drug for urgent rate control and possibly, cardioversion of AF. Tecadenoson terminated 86.5% paroxysmal supraventricular tachycardias in the proof-of-concept study in 37 patients presenting predominantly with atrioventricular nodal re-entrant tachycardia.<sup>102</sup> In the phase III TEMPEST (Trial to Evaluate the Management of Paroxysmal supraventricular tachycardia during Electrophysiological Study with Tecadenoson), the drug converted 50–90% of the induced supraventricular tachycardias without causing significant adverse symptoms.<sup>103</sup> Tecadenoson has recently entered a phase IIb study in patients with AF or atrial flutter.

#### Selodenoson

*Selodenoson* (DTI-0009, Aderis Pharmaceuticals) is another adenosine-like agent which differs from tecadenoson in

that it has a longer half-life (150 min) and appears more suitable for oral application. In the double-blind, placebo-controlled trial of 63 patients, all six administered doses of selodenoson demonstrated a statistically and clinically significant decrease in ventricular rate compared with placebo.<sup>104</sup> Final results are pending from three other phase II trials in patients with spontaneous AF with uncontrolled ventricular rates. A sustained release formulation of DTI-0009 is in phase I development.

## Gene and cell-specific therapies

Evolution of the current knowledge of specific ion channels and proteins pivotal in arrhythmogenesis has stimulated research into potential gene and cell-based therapies which can selectively target individual currents and ideally, would provide one-time curative therapy for arrhythmias. In AF, strategies have been explored to modulate atrioventricular conduction by creating a genetic calcium blocker. In these proof-of-concept experiments, the  $I_{CaL}$  current in the atrioventricular nodal cells was inhibited by the transfer of the adenoviral vector carrying inhibitory G $\alpha_{i2}$  protein<sup>105</sup> or by the targeted gene transfer of a Ras-related small G protein (Gem) which regulates trafficking of the  $I_{CaL}$   $\alpha$ -subunit to sarcolemma.<sup>106</sup> In pigs with persistent (3 weeks) AF, the ventricular response rate to induced AF was decreased by 15–25%, initiating reversal remodelling.<sup>105</sup> Following identification of mutations in several genes encoding proteins that constitute potassium and sodium channels in patients with familial AF, the atrial  $I_{Kr}$  current has been selectively modified by a direct application of adenoviral vectors expressing a long QT syndrome gene mutant (HERG-G628S) to the epicardial surface of porcine atria.<sup>107</sup> HERG-G628S gene transfer caused a homogeneous prolongation of atrial action potential duration, without affecting the ventricles.

## Conclusion

In summary, there are several new pharmacological agents that may shortly be released for the management of AF and many others that are currently under clinical investigation. New anti-arrhythmic drugs targeting multiple channels or having a specific high affinity to the atrial myocardium are believed to have a more favourable risk–benefit ratio than traditional anti-arrhythmic drugs. As a broader perspective develops regarding the systemic, organ, tissue, myocyte membrane, and intra-cellular contributions to the genesis of AF, new therapies, such as gap junction modulators, stretch receptor antagonists, and effective upstream anti-inflammatory and anti-fibrotic therapy, may offer a much more comprehensive and effective anti-arrhythmic strategy than is currently available.

**Conflict of interest:** J.C. is consultant to sanofi aventis, Cardiome, Astellas and Xention.

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