

## Status of Antiarrhythmic Drug Development for Atrial Fibrillation New Drugs and New Molecular Mechanisms

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a lifetime risk exceeding 20% by 80 years of age.<sup>1</sup> AF is associated with a significant burden of morbidity and increased risk of mortality.<sup>2</sup> Even with advances in catheter ablation procedures, antiarrhythmic drug therapy remains a cornerstone in the treatment of AF both to restore and maintain sinus rhythm. However, most are of modest efficacy and have significant side effects (Table). Antiarrhythmic drug development has remained slow, despite much effort given our limited understanding of what role various ionic currents play in arrhythmogenesis and how they are modified by arrhythmias.<sup>3</sup> In addition, potentially life-threatening hazards (proarrhythmia) and significant noncardiac organ toxicity have posed a challenge for new drug development. Multichannel blockade, atrial selectivity, and the reduction of the risk of adverse events have all constituted the main theme of modern AF drug development with a shift in emphasis to include composite clinical end points rather than arrhythmia suppression alone.<sup>4</sup> In this article, we will focus on recent advances in drug therapy for AF, reviewing molecular mechanisms, and the possible clinical use of novel antifibrillatory agents.

### Cardioversion

Advantages of using drug therapy over direct current cardioversion for AF include avoiding the need for general anesthesia or conscious sedation, a potentially lower risk of immediate AF recurrence and arguably reduced psychological stress for the patient.<sup>5</sup> Ibutilide and dofetilide are currently licensed for the use in AF cardioversion, but are limited by their side effect of QT prolongation and, therefore, possible induction of Torsade de Pointes. Amiodarone and class Ic antiarrhythmics such as flecainide are also used for cardioversion, but are limited by delayed onset of action and ventricular proarrhythmia, respectively.

There is therefore an unmet need to find safe and effective drugs that can rapidly cardiovert AF. Two such drugs that have been recently developed are vernakalant and vanoxerine, both of which demonstrate frequency-dependent block of sodium (Na) channels, leading to atrial selectivity. This refers to more potent Na channel blockade in the atria compared

with the ventricles because of electrophysiological differences between the chambers, rather than the use of an atrial-specific ion channel.

### Vernakalant

Vernakalant was originally developed to target the atrial-specific ultrarapid delayed rectifier K<sup>+</sup> current (I<sub>Kur</sub>). However, it is a multichannel blocker inhibiting I<sub>Kur</sub>, the transient outward potassium current (I<sub>to</sub>), the peak and late Na currents, the rapidly activating delayed rectifier potassium channels (I<sub>Kr</sub>), and the inward-rectifying potassium channels (I<sub>KAch</sub> and I<sub>KATP</sub>). It is now thought that although I<sub>Kur</sub> block may contribute to vernakalant's antifibrillatory effect, its most important action is through atrial-selective blockade of the peak sodium current.<sup>6</sup> The effective refractory period is made shorter during AF, and lengthening the effective refractory period can lead to AF termination. This can be achieved by prolonging the action potential duration (APD), primarily by inhibiting potassium channels, or by blocking sodium channels, which increases cardiac excitation threshold, slows conduction, and creates a period of refractoriness after the action potential has repolarized without significant prolongation of APD, making this method less proarrhythmic. This effect is called postrepolarization refractoriness and has been observed in studies of the action potential using paced canine atrial wedge preparations.<sup>6</sup>

The electrophysiological differences between the atria and ventricles and the specific properties of vernakalant allow inhibition of the peak sodium current to be its dominant effect during AF. Work by Antzelevitch et al<sup>6,7</sup> provide a useful and detailed discussion of these electrophysiological differences leading to atrial-selective blockade of the peak sodium current. Importantly, the fact that vernakalant also inhibits the late sodium current means that any effects of I<sub>Kr</sub> blockade on prolonging the APD in the ventricles is offset, therefore, lowering the risk of ventricular arrhythmia.<sup>6</sup>

These properties of vernakalant would predict a beneficial efficacy and safety profile in clinical practice, and indeed this has been reflected in clinical studies. To our knowledge, there have been 5 double-blind, randomized control trials (DB-RCT) on the use of vernakalant for AF cardioversion:

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Atrial Arrhythmia Conversion Trial (ACT) I,<sup>8</sup> ACT II,<sup>9</sup> ACT III,<sup>10</sup> CRAFT (Conversion of Rapid Atrial Fibrillation Trial),<sup>11</sup> and A Phase III Superiority Study of Vernakalant Versus Amiodarone in Subjects With Recent Onset Atrial Fibrillation (AVRO).<sup>12</sup> All used a placebo as the control arm, except the AVRO trial, which compared vernakalant with amiodarone. A meta-analysis of these trials by Buccelletti et al<sup>13</sup> showed that vernakalant had a significantly increased cardioversion rate within 90 minutes of administration ( $P \leq 0.00001$ ) and no significant difference in adverse events compared with placebo/amiodarone. A later meta-analysis<sup>14</sup> that included these DB-RCTs as well as 2 observational studies comparing vernakalant with amiodarone<sup>15</sup> and flecainide,<sup>16</sup> respectively, demonstrated that vernakalant had a statistically superior efficacy to placebo, but not to other antiarrhythmic drugs during pooled analysis. However, individual studies comparing vernakalant with amiodarone, flecainide and propafenone have shown superior efficacy for vernakalant. Vernakalant has also been shown to have similar efficacy to direct current cardioversion in an observational comparison study.<sup>17</sup> As predicted from the basic science discussed above, vernakalant use did not result in an increased incidence of ventricular arrhythmia compared with placebo. Those patients that did develop clinically significant ventricular arrhythmia after vernakalant were more likely to have heart failure and valvular heart disease.<sup>5</sup>

The faster time to cardioversion for vernakalant and its rapid clearance from the body (roughly 2 hours)<sup>18</sup> makes this an ideal drug for chemical cardioversion in the acute hospital setting or emergency department. A study by Lamotte et al<sup>19</sup> in a Belgian emergency department found that the use of vernakalant was cost saving compared with direct current cardioversion or amiodarone. Vernakalant has been approved in Europe for the cardioversion of AF of <3 days duration in postoperative patients and <7 days in patients who are not postoperative.<sup>20</sup>

The Food and Drug Administration has not yet approved vernakalant because it recommended a large randomized control trial to better assess the efficacy and safety profile of the drug. Unfortunately this study, ACT V, was prematurely terminated because of a death secondary to severe cardiogenic shock in the vernakalant arm.<sup>13</sup> However, it is not certain that this

death is directly attributable to drug administration. Because there have been many adverse events attributed to vernakalant in case reports, such as hypotension,<sup>6</sup> and possible precipitation of atrial flutter<sup>21,22</sup> or atrial tachycardia<sup>23</sup> with 1:1 conduction, the relative risk of infrequent adverse events can only be better assessed in a large randomized trial, perhaps comparing vernakalant directly with direct current cardioversion.

### Vanoxerine

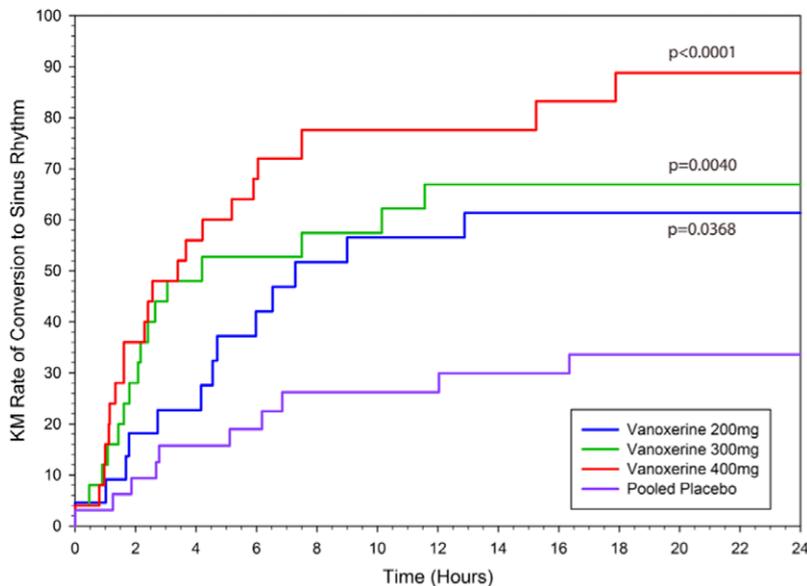
Vanoxerine is a 1,4-dialkylpiperazine derivative, originally developed for Parkinson disease as a dopamine transporter 1 antagonist. It has been shown to potently inhibit the  $I_{Kr}$ ,  $I_{Na}$ , and L-type Ca ( $I_{Ca(L)}$ ) currents using whole cell patch clamp techniques.<sup>24</sup> Interestingly, the degree of channel block was found to be use-dependent for all 3 ion channels, particularly  $I_{Na}$  and  $I_{Ca(L)}$ . Therefore, similar to vernakalant, the electrophysiological differences between atria and ventricles favor a greater therapeutic effect in the atria during AF. Experiments with canine ventricular wedge preparations demonstrated that vanoxerine did not prolong the QT interval and did not affect the action potential waveform or the transmural dispersion of repolarization, therefore, it is less likely to induce ventricular arrhythmia.<sup>24</sup>

There has been 1 DB-RCT assessing the use of vanoxerine for the chemical cardioversion of recent-onset AF: the COR-ART trial.<sup>25</sup> This was a multicentre, phase 2b trial, involving 104 patients. It demonstrated that oral vanoxerine at the 300 and 400 mg doses had statistically increased cardioversion rate compared with placebo (Figure 1). The overall efficacy of cardioversion was 85%. The side effects experienced in the vanoxerine arms were mild and self-limiting and despite it prolonging the QTc interval in humans, there were no incidences of monomorphic or polymorphic ventricular tachycardia. The disparity between the QTc prolongation seen in the COR-ART study compared with the wedge experiments is likely explained by the fact that the wedge preparations were tested at basic cycle lengths of 1 and 2 s, whereas the ventricular rates in the COR-ART were likely to be higher, permitting a greater degree of use-dependent  $I_{Kr}$  block in the ventricles, and hence QTc prolongation. Vanoxerine's lack of effect on

**Table. Vaughn–Williams Classification of Currently Used Antiarrhythmic Drugs**

Class	Example drugs	Mechanism of action	Limitations
1a	Quinidine Procainamide Lidocaine	$I_{Na}$ inhibition (intermediate kinetics) $I_{Kr}$ inhibition	Risk of TdP, associated with possible increased mortality
1b	Lidocaine Mexilitine	$I_{Na}$ inhibition (fast kinetics)	No efficacy in atrial arrhythmias
1c	Flecainide Propafenone	$I_{Na}$ inhibition (slow kinetics)	Contraindicated in CAD and structural heart disease
II	$\beta$ -Blockers	B-adrenergic receptor antagonist	Hypotension, bradycardia
III	Amiodarone Dofetilide Sotalol	Multichannel blocker $I_{Kr}$ inhibition $I_{Kr}$ inhibition	Extra-cardiac side effects Risk of TdP, dependent on renal clearance
IV	Nondihydropyridine calcium channel blockers	$I_{Ca(L)}$ inhibition	Hypotension, bradycardia

CAD indicates coronary artery disease; and TdP, Torsades de Pointes.



**Figure 1.** Kaplan–Meier (KM) plot of time to restoration of sinus rhythm (COR-ART, n=104). *P* values: log-rank test results for time to conversion vs placebo. Reprinted from Dittrich et al<sup>25</sup> with permission of the publisher. Copyright © 2015, Elsevier.

transmural dispersion of repolarization observed in the wedge preparations, may explain the lack of ventricular arrhythmias in COR-ART, despite QTc prolongation.

What is also reassuring from a safety perspective is that the study population included patients with structural heart disease, therefore, vanoxerine could prove useful for cardioversion in many patients currently excluded from using class IC drugs.

## Rate Control

### Ivabradine

The funny current,  $I_f$ , is a mixed sodium–potassium current that activates with membrane hyperpolarization, as opposed to activation with depolarization.  $I_f$  was originally thought to be present only in the sinoatrial node. However, more recent data have shown functional expression in the atrioventricular node as well, suggesting that drugs that block this current may be a novel means of modulating atrioventricular nodal conduction.<sup>26</sup>

Ivabradine, the prototypical  $I_f$  inhibitor, has been shown to operate only during the open state, when the compound enters the channel pore from the intracellular side to bind the ion permeation pathway.<sup>27</sup> Accordingly, the drug is most effective when there are rapid cycles of channel opening and closing, as occur at high heart rates. Ivabradine was recently approved in the United States to reduce the risk of hospitalization in chronic heart failure patients with sinus rhythm heart rate of >70 per minute on maximally tolerated  $\beta$ -blockers.

In a recent study, the effects of ivabradine were studied in anesthetized Yorkshire pigs and in isolated guinea pig hearts.<sup>28</sup> Verrier et al<sup>28</sup> demonstrated that ivabradine exerts a marked rate-dependent slowing of atrioventricular node conduction during AF, reflected in an increase in A–H interval that was inversely correlated with ventricular rate. This study provides significant preclinical evidence that ivabradine may have a role in AF rate control. Subsequently, several cases have been published demonstrating significant heart rate reduction with the off label use of ivabradine in patients with AF.<sup>29,30</sup> However, these are isolated cases and further randomized controlled

trials are warranted. In addition, because AF is known to be a side effect of ivabradine treatment, its use for rate control would likely be limited to patients with chronic AF rather than those with paroxysmal AF.<sup>31</sup>

## Maintenance

### Canakinumab

Although predisposing factors such as hypertension, diabetes mellitus, valvular heart disease, and heart failure are found in most patients with AF,  $\approx 12\%$  of AF cases are free of coexisting diseases.<sup>32</sup> Elevated markers of inflammation such as C-reactive protein, interleukin-1 (IL-1), IL-6, tumor necrosis factor, and inflammatory changes in histopathologic examination of atrial tissues showed that chronic inflammation may play a role in AF initiation and perpetuation.<sup>33–36</sup> Polymorphisms of IL-1 $\beta$  have been associated with AF likely because of the inadequate limitation of inflammatory reactions.<sup>37</sup>

Canakinumab is a human monoclonal antibody that selectively neutralizes the proinflammatory cytokine IL-1 $\beta$ . Canakinumab significantly reduces systemic C-reactive protein and other inflammatory biomarker levels, is generally well tolerated, and is currently indicated for the treatment of inherited IL-1 $\beta$ -driven inflammatory diseases.<sup>38</sup> It is currently being studied for the prevention of recurrences of AF after electric cardioversion in patients with persistent AF in the Canakinumab for the Prevention of Recurrences After Electrical Cardioversion (CONVERT-AF) trial.<sup>39</sup> One 150 mg subcutaneous injection administered immediately after electric cardioversion is being compared with placebo for time to recurrence of AF. If positive, CONVERT-AF would further validate the inflammatory contribution to AF and provide a novel cytokine-based therapy.

### Xention-D0101 and Xention-D0103/S66913

Xention-D0101 is selective antagonist of the potassium channel Kv1.5. It has been demonstrated to prolong atrial refractoriness and suppress AF in canine models, with similar electrophysiological effects on isolated human atrial

myocytes.<sup>40,41</sup> It has been assessed in a phase 1 study to establish the safety of modulating the Kv1.5 target in vivo and is currently being assessed in a proof-of-mechanism electrophysiology phase 1 study at multiple European sites.<sup>42</sup>

XEN-D0103/S66913 is more potent and more selective than XEN-D0101 and has recently completed preclinical development. It causes a significant extension of the APD in atrial tissue, but has no effect on the APD in human ventricular tissue.<sup>43</sup> A phase 2 study, XAPAF (Beat to Beat Efficacy Study of XEN-D0103, a Novel IKur Blocker, in Patients With Paroxysmal Atrial Fibrillation and Permanent Pacemakers), is underway to assess the efficacy and safety of XEN-D0103/S66913 in patients with paroxysmal AF. The design is a double-blind, randomized, placebo-controlled, crossover trial patients having paroxysmal AF who also have implanted pacemakers, enabling continuous monitoring of drug efficacy. A second phase 2 trial, DIAGRAF-I<sub>Kur</sub> (IKur–Double-Blind, International Study Assessing Efficacy of S 066913 in Paroxysmal Atrial Fibrillation–IKur Inhibitor), is currently under review and expected to begin in the near future.

### Ranolazine+Dronedaronone

A new line of investigation in the field of antiarrhythmic therapy uses combinations of currently approved medications. These combinations offer improved efficacy in a synergistic manner, which may allow for the use of reduced doses of each compound and thereby reduced side effects.

Ranolazine is predominantly a late Na<sup>+</sup> current (I<sub>Na</sub>) blocker, with effects on I<sub>Kur</sub> as well.<sup>44,45</sup> Evidence suggest that late I<sub>Na</sub> is increased in patients with AF and ranolazine has been shown to be capable of reversing such late I<sub>Na</sub> current upregulation.<sup>46</sup>

Dronedaronone is a benzofuran derivative with an electropharmacologic profile resembling that of amiodarone but with different relative effects on individual ion channels.<sup>47–50</sup> The structural changes made to amiodarone to produce dronedaronone include the removal of iodine and the addition of a methanesulfonfyl group.

Low-dose dronedaronone and ranolazine separately, only modestly affect APD and repolarization. However, the combination has been shown to have a dramatic effect beyond what would be expected by adding the effects of the 2 drugs.<sup>51</sup> This synergistic effect allows for lower dosing of dronedaronone, thereby reducing its effect on cardiac contractility. In addition, the slowly activating delayed rectifier K<sup>+</sup> current (I<sub>Ks</sub>) becomes more dominant at high frequencies. So, in AF a proportionately higher amount of I<sub>Ks</sub> is blocked and the net result with low-dose dronedaronone is minimized effect on I<sub>Ca(L)</sub>, with increased frequency-dependent block of I<sub>Na</sub> and I<sub>Ks</sub>.<sup>52</sup>

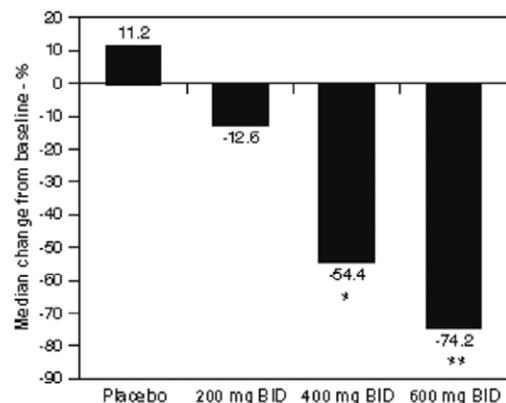
In the phase 2 clinical trial, HARMONY (A Study to Evaluate the Effect of Ranolazine and Dronedaronone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation),<sup>53</sup> 134 patients were randomized to 1 of 5 treatment arms: placebo, ranolazine 750 mg tablet twice daily, dronedaronone 225 mg capsule twice daily, ranolazine 750 mg/dronedaronone 150 mg (RD150) twice daily, or ranolazine 750 mg/dronedaronone 225 mg (RD225) twice daily. The primary end point was change in AF burden during 12 weeks. AF burden was defined as the total time a patient was in atrial tachycardia/AF expressed

as percentage of total recording time continuously from 0 to 12 weeks. Patients in the RD150 and RD225 arms experienced respective reductions of 45% and 59% in AF burden from baseline during 12 weeks ( $P=0.072$  and  $P=0.008$ , respectively, versus placebo). Among patients receiving RD225, 45% achieved AF burden reductions from baseline of  $\geq 70\%$  during 12 weeks. Neither ranolazine nor dronedaronone alone caused statistically significant reductions in AF burden from baseline compared with placebo. There was no clinically significant difference between treatment groups in the overall incidence of adverse events or adverse events leading to discontinuations.

### Budiodarone

Budiodarone is an amiodarone analog that maintains iodine moieties but contains an ester modification that allows extensive metabolism by tissue esterases rather than by hepatic cytochromes. As a result, the half-life of budiodarone is significantly shorter than that of amiodarone (7 hours), whereas electrophysiological properties are similar.<sup>54</sup> Only limited clinical data on budiodarone are available. Thus far, there have only been 2 published studies investigating the use of budiodarone in humans. The first study was a report in 6 female patients with paroxysmal AF and dual chamber pacemakers.<sup>55</sup> The primary end point was AF burden defined as percent of time in AF based on pacemaker interrogation. Patients received placebo, 200, 400, 600, and 800 mg twice daily dosing of budiodarone in sequential 2-week periods. Budiodarone was found to have a statistically significant reduction in the total burden of AF with all doses compared with placebo.

These encouraging results were confirmed in a phase II clinical trial, the Paroxysmal Atrial Fibrillation Study with Continuous Atrial Fibrillation Logging (PASCAL).<sup>56</sup> Seventy-two patients were randomized to placebo, 200, 400, or 600 mg of budiodarone twice daily for 12 weeks. Again, the primary end point was AF burden determined by dual chamber pacemaker interrogation. The investigators found a dose–response relationship wherein the 400 and 600 mg doses significantly reduced AF burden compared with placebo (Figure 2). In this study, both the frequency of AF episodes and the duration of episodes were reduced with budiodarone.



**Figure 2.** Percent change (median) in atrial tachycardia/atrial fibrillation burden from baseline to 3 months.  $P<0.001$  for dose response. \* $P<0.05$  for budiodarone vs placebo. \*\* $P<0.01$  for budiodarone vs placebo. Reprinted from Ezekowitz et al<sup>56</sup> with permission of the publisher. Copyright © 2011, Springer.

With regard to safety, patients in the bupropion group experienced an increase of thyroid-stimulating hormone, reversible after drug discontinuation. An increase in serum creatinine levels was also reported, probably because of a bupropion-like inhibitory effect on renal organic cation transport. No QT prolongation was observed during the study course. However, the selection of patients with a permanent pacemaker may have limited the evaluation of some of the possible side effects of bupropion, such as depression of atrioventricular conduction velocity.

This limited experience with bupropion is intriguing, however, further studies on broader populations of patients and with longer follow-up durations are necessary to better evaluate the effectiveness and safety of this new drug in AF.

### Moxonidine

There is substantial evidence that the autonomic system plays an important part in the pathogenesis of AF.<sup>57</sup> Some patients have a predominantly sympathetic or vagal overactivity leading to AF, however, a combined sympathovagal activation is most commonly responsible for AF triggering.<sup>58,59</sup> Modulation of the autonomic system and its sympathetic limb, in particular, is of therapeutic interest in AF. Moxonidine is a centrally acting sympathoinhibitory agent. In prospective, double-blinded, single-group, crossover study, 56 hypertensive patients with paroxysmal AF sequentially received treatment with placebo and moxonidine for two 6-week periods, respectively.<sup>60</sup> The change in AF burden, measured as minutes of AF per day in three 48-hour Holter recordings, between the 2 treatment periods was the primary outcome measure. During moxonidine treatment, AF burden was reduced from 28 to 16.5 min/d and European Heart Rhythm Association symptom severity class decreased from a median of 2.0 to 1.0. Systolic blood pressure levels were similar in the 2 treatment periods, whereas diastolic blood pressure was lower ( $P<0.01$ ) during moxonidine treatment. No serious adverse events were recorded.

This was a small study, whose main aim was to prove the principle that pharmacological modulation of the central sympathetic tone may be of therapeutic use in patients with paroxysmal AF. One cannot exclude, however, the possibility that the reduction in diastolic blood pressure levels observed during moxonidine treatment may be responsible, at least in part, for the decrease in AF burden. In addition, these results should not be extrapolated to the general population of patients with AF. Patients with impaired ventricular function were excluded according to the results of the Moxonidine in Congestive Heart Failure (MOXCON) trial, in which moxonidine was found to have a deleterious effect in patients with heart failure and an ejection fraction of  $<0.35$ .<sup>61</sup> However, further investigation of the potential role of moxonidine in the treatment of AF in relevant patient populations should be pursued.

### Maintenance Post Ablation

#### Colchicine

After catheter ablation, leukocytosis and proinflammatory cytokines have been directly related to the incidence of postprocedural AF.<sup>62</sup> As the cytokines increase, the risk of AF concomitantly increases. Therefore, colchicine, a potent

anti-inflammatory agent, may have a relevant role in preventing inflammatory-facilitated AF after catheter ablation. Colchicine is thought to act through inhibition of microtubule assembly in cells of the immune system, particularly neutrophils, leading to inhibition of several cellular functions, including cytokine production by these cells.<sup>63</sup> Its method of action includes modulation of chemokine and prostanoid production and inhibition of neutrophil and endothelial cell adhesion molecules.<sup>64</sup>

In a double-blind, placebo-controlled study, patients with paroxysmal AF who received radiofrequency ablation treatment were randomized to a 3-month course of colchicine 0.5 mg twice daily or placebo.<sup>65</sup> After 3 months, recurrence of AF was observed in 27 (33.5%) of 80 patients of the placebo group versus 13 (16%) of 81 patients who received colchicine (odds ratio, 0.38; 95% confidence interval, 0.18–0.80). Colchicine led to higher reductions in C-reactive protein and IL-6 levels compared with placebo.

Given these encouraging results, the group published an extension of the previous study in which they reported the midterm efficacy of colchicine.<sup>66</sup> Two hundred twenty-three randomized patients underwent ablation and 206 patients were available for analysis. AF recurrence rate in the colchicine group was 31.1% (32/103) versus 49.5% (51/103) in the control group ( $P=0.010$ ). In addition to the anti-inflammatory effects of colchicine, the antimitotic action of colchicine may also play a role in its effect on AF recurrence rate. Recovery of conduction between the atrium and the pulmonary veins is a common finding in patients with AF recurrence after ablation, even if pulmonary vein isolation was adequately documented during the procedure.<sup>67,68</sup> Recovery of conduction may be due, in part, to local tissue regeneration in nontransmural ablation lesions and reversibility of thermal injury seems to be an important determinant of recovery of conduction.<sup>69</sup> Colchicine could intervene in this process through its antiproliferative action, inhibiting electric reconnection in thermal injury ablation sites.

### Moxonidine

As previously mentioned, autonomic system activation has increasingly been recognized as an important factor in the genesis of AF. The centrally acting sympathoinhibitory agent, moxonidine, was tested in a prospective, double-blinded, randomized, controlled study of hypertensive patients with symptomatic paroxysmal AF undergoing pulmonary vein isolation.<sup>70</sup> Patients were randomly assigned to receive either moxonidine (0.2–0.4 mg daily) or placebo, along with standard antihypertensive treatment. The primary outcome was time to AF recurrence after a 3-month blanking period. The mean recurrence-free survival was 467 days in the moxonidine group when compared with 409 days in control subjects ( $P=0.006$ ). The calculated 12-month recurrence rate estimates were 36.9% in the control group and 20.0% in the moxonidine group ( $P=0.007$ ). Moxonidine treatment was associated with lower recurrence risk after adjustment for age, body mass index, number of AF episodes in the previous year, and left atrial diameter. No significant differences in blood pressure levels were observed between the 2 groups. Therefore, treatment with moxonidine was associated with less AF recurrences after pulmonary vein isolation and the observed effect did not seem to depend on its antihypertensive action. On

the basis of the results of this study, further investigation is warranted.

### Pharmacogenetics

Pharmacogenetic effects have recently been highlighted as an important factor in the treatment of AF. The Beta-Blocker Evaluation of Survival Trial (BEST) was designed to determine whether bucindolol, a nonselective  $\beta$ -adrenergic blocker and mild vasodilator, would reduce the rate of death from any cause among patients with advanced heart failure. Although the overall study was negative, it was found that genetic polymorphisms of the  $\beta_1$ -adrenoreceptor ( $B_1AR$ ) actually influenced the efficacy of the bucindolol in this population.<sup>71,72</sup>

Twelve single-nucleotide polymorphisms have been identified in the  $B_1AR$ , but only 2 of these are thought to be clinically relevant. At position 389, the glycine nucleotide in the G-protein coupling domain can be substituted for arginine.<sup>73</sup> This is a gain of function polymorphism, resulting in increased adenylate cyclase activity. The Arg/Arg genotype is associated with increased sensitivity of the ADRB1 receptors to noradrenaline,<sup>74</sup> a 3- to 4-fold increase in signal transduction and an increase in the number of constitutionally active receptors compared with the Arg/Gly or Gly/Gly genotypes.<sup>75</sup> The other important  $B_1AR$  polymorphism is at position 49 of the  $B_1AR$  and is thought to have a modulating role in adenylate cyclase activity.<sup>73</sup>

The gain of function Arg/Arg polymorphism is important because higher adrenergic activity has been shown to increase the likelihood of AF induction in a dose-dependent manner.<sup>76</sup> Bucindolol acts as a competitive antagonist of the  $B_1AR$ , facilitates the inactivation of constitutionally active receptors (inverse agonism), and decreases levels of noradrenaline.<sup>71</sup> The substudy of the BEST by Aleong et al<sup>71</sup> demonstrated that bucindolol prevented new-onset AF in patients with heart failure with reduced ejection fraction in 74% of patients with the Arg/Arg genotype, but had no effect in those patients with the Gly/Gly genotype. The substudy by Kao et al<sup>72</sup> also found that all-cause and cardiovascular mortality, as well as cardiovascular and heart failure hospitalizations were significantly reduced in patients with the Arg/Arg genotype, but not glycine carriers. The enhanced adrenergic signaling in the Arg/Arg genotype may render it more susceptible to bucindolol's sympatholytic actions, thereby preventing the induction of AF that might normally occur in these patients.

Interestingly, a study by Parvez et al<sup>77</sup> demonstrated that the loss of function glycine 389 polymorphism is associated with a significantly better response to rate-controlling therapies in patients with AF. This may be explained because the rate-control therapies can work synergistically with the attenuated  $\beta_1$ -adrenergic cascade caused by this genotype.

Adrenoceptor polymorphisms may also influence the efficacy of other antiarrhythmic drugs used for AF. A study by Nia et al demonstrated that the conversion rate of AF with flecainide was highest in patients with the Arg/Arg genotype and lower in glycine carriers.<sup>73</sup> Patients who were glycine carriers did, however, have lower heart rates during AF, corroborating the findings by Parvez et al.<sup>77</sup>  $B_1AR$  polymorphisms may alter the efficacy of flecainide because adrenoceptor stimulation induces sodium channel inhibition;<sup>73</sup> therefore, the enhanced adrenergic signaling associated with the Arg/Arg

polymorphism may synergistically inhibit sodium channels with flecainide. This adrenergic influence on sodium channels might also explain why the ACT I trial found that patients who had their AF successfully cardioverted with the sodium channel blocker vernakalant had a higher baseline heart rate, which is associated with the Arg/Arg polymorphism.<sup>8</sup>  $B_1AR$  polymorphisms could also influence the efficacy of amiodarone because it possesses antiadrenergic effects.<sup>78</sup> The pharmacogenetic properties of antiarrhythmic drugs are, therefore, an important area for further research to further understand which patients will benefit from both existing and novel therapies for AF.

### Conclusions

Antiarrhythmic medications are essential in managing patients with AF. In the coming years, novel pharmacological strategies will become available to treat AF. Beyond demonstrating drug effectiveness, research should continue to focus on safety as well as identifying the subset of patients who may earn the greatest benefit.

### Disclosures

Dr Kowey has served as a consultant for Medtronic, Boston Scientific and St. Jude as well as Astellas, ChanRx, Amgen, Servier, Sanofi, Pfizer, and Gilead. The other authors report no conflicts.

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KEY WORDS: amiodarone ■ atrial fibrillation ■ catheter ablation ■ flecainide ■ vernakalant

## Status of Antiarrhythmic Drug Development for Atrial Fibrillation: New Drugs and New Molecular Mechanisms

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