New Pharmacological Agents for Arrhythmias

Pamela K. Mason, MD; John P. DiMarco, MD, PhD

Despite advances in catheter ablation techniques and device-based therapies for cardiac arrhythmias, antiarrhythmic drugs remain essential components of any comprehensive therapeutic strategy. Antiarrhythmic drug therapy, however, has been limited by both incomplete efficacy and a substantial potential for cardiac and extracardiac toxicity. As a result, only a few new antiarrhythmic agents have successfully completed clinical development programs and reached routine clinical usage over the past 20 years.

Antiarrhythmic drugs may be indicated for ventricular tachycardia, sudden death prevention, or specific types of supraventricular arrhythmia. Implantable cardioverter-defibrillator (ICD) therapy has evolved as the primary treatment for most life-threatening ventricular arrhythmias, and antiarrhythmic drugs for these rhythms are currently mostly used either as acute interventions or as adjuncts to chronic ICD therapy. Although numerous trials have evaluated the effect of antiarrhythmic drugs to decrease ICD shocks or therapies, such data have yet to provide the sole basis for approval for any new agent. At the same time, drug therapy for atrial arrhythmias is often limited by the drug’s simultaneous effects on the ventricles, which has led to efforts to identify ionic channel targets specific to or preferentially simultaneous and induced ventricular fibrillation.

Agents Similar to Amiodarone

Amiodarone is generally accepted to be a valuable antiarrhythmic drug, but it accumulates in tissues during long-term therapy, which may result in significant toxicity in several organ systems. Several compounds that were designed to be similar in structure and electrophysiological effects to amiodarone have completed or are now in clinical trials.

Dronedarone

Dronedarone is, like amiodarone, a benzofuranyl compound with iodine removed and a methane sulfonyl group added (Figure 1). Removing iodine from the molecule was intended to eliminate or reduce iodine-related organ toxicity. The side chain modification decreased lipophilicity, resulting in a shorter elimination half-life with less potential for tissue accumulation. The basic and clinical pharmacology of dronedarone has been recently reviewed.6

Dronedarone retains many of amiodarone’s electrophysiological effects. It is a multichannel blocker with effects on the rapid and slow components of the delayed rectifier current ($I_{K_r}$ and $I_{K_s}$), L-type calcium currents ($I_{Ca,L}$), the inward sodium current ($I_{Na}$), and the inward rectifier potassium current ($I_K$). Dronedarone also inhibits the acetylcholine receptor-dependent K+ current ($I_{K_ACh}$) and the pacemaker current ($I_p$) and is a noncompetitive α- and β-adrenergic antagonist. Dronedarone reduces sinus rate and prolongs AV nodal conduction and refractoriness. Effects on the QT and QTc intervals have been variable when studied in different species. In several animal models of ischemia or reperfusion-induced arrhythmias, dronedarone effectively prevents spontaneous and induced ventricular fibrillation.

The pharmacokinetic properties of dronedarone are complex.7 Dronedarone is well absorbed after oral ingestion but undergoes extensive first-pass metabolism mediated by CYP3A4, resulting in a net bioavailability of only 15% when taken with meals. Several metabolic pathways are active, including N-debutylation, oxidative N-deamination, and direct oxidation. The steady-state elimination half-life for dronedarone is estimated to be 13 to 24 hours. The N-debutyl derivative (SQ35021A) is electrophysiologically active but less potent than the parent compound. In the large clinical trials, using 400 mg twice daily, the trough plasma concentration at steady state has been 60 to 150 ng/mL. Potent CYP3A4 inhibitors (eg, ketoconazole, erythromycin, etc) can markedly increase dronedarone plasma concentrations. Less potent CYP3A4 inhibitors (eg, diltiazem, verapamil, moderate amounts of grapefruit juice, etc) produce lesser effects. Potent CYP3A4 inducers (eg, rifampin, phenytoin, St John’s

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Dronedarone, etc) should not be used with dronedarone. Dronedarone inhibits both CYP3A4 and CYP2D6. Interactions with CYP3A4 substrates (eg, many statins and calcium antagonists) are possible and should be considered. Dronedarone does not inhibit CYP2C9 or CYP2C19, and interactions with warfarin have not been reported. Dronedarone increases serum digoxin levels by inhibiting P-glycoprotein–mediated renal excretion. Dronedarone also inhibits renal organic cation transport, and this effect may cause serum creatinine levels to rise without decreasing glomerular filtration as measured by inulin clearance. Dronedarone should not be used in patients with severe hepatic dysfunction. Dosage reduction is not required in patients with renal insufficiency.

Clinical Studies

Dronedarone has been studied in a series of double-blinded, randomized trials in patients with atrial fibrillation (Table 1).

The Dronedarone Atrial Fibrillation Study After Electric Cardioversion (DAFNE) evaluated 3 doses of dronedarone (400, 600, and 800 mg twice daily) in 270 patients with persistent atrial fibrillation. Hypertensive, valvular, and ischemic heart disease were the most common cardiac diagnoses. Pharmacological conversion during the initial 5 to 7 days of therapy was observed in 3.1%, 5.8%, 8.5%, and 14.8% of the placebo, 400, 600, and 800 mg twice daily groups, respectively. Seventy-one patients in all could not be electrically cardioverted, but there was no significant difference in combined pharmacological and electric cardioversion success between the groups. Among the 199 patients in whom sinus rhythm could be restored, 400 mg dronedarone but not the 600 mg or 800 mg twice-daily doses significantly prolonged the time to first recurrence from a median of 5.3 days in the placebo group to 60 days in the dronedarone group. At 6 months, 35% of patients in the dronedarone group had maintained sinus rhythm compared with only 10% of the placebo patients. Time to first recurrence was slightly but not significantly delayed in the 600 mg or 800 mg twice-daily dose groups. This lack of dose response was unexplained. If atrial fibrillation recurred, the ventricular rate was reduced by 13% in the 400 mg twice-daily group.

The combined European and American-Australian-African Trials In Atrial Fibrillation or Flutter Patients in the Maintain-

Table 1. Major Clinical Trials of Dronedarone in Patients With Atrial Fibrillation

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Entry Criteria</th>
<th>Dronedarone Dose</th>
<th>Comparator</th>
<th>Primary End Point</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAFNE9</td>
<td>199</td>
<td>Post-CV</td>
<td>200, 400, 600 mg twice daily</td>
<td>Placebo</td>
<td>Time to first AF</td>
<td>With 400 mg twice daily: prolonged time to AF recurrence (60 vs 5.3 d); more sinus rhythm at 6 mo (35% vs 1%)</td>
<td>Loss of benefit at 600 and 800 mg twice daily</td>
</tr>
<tr>
<td>EURIDIS and ADONIS10</td>
<td>1237</td>
<td>Post-CV</td>
<td>400 mg twice daily</td>
<td>Placebo</td>
<td>Time to first AF</td>
<td>Prolonged time to AF recurrence (116 vs 53 days); total recurrence decreased (64% vs 75%)</td>
<td></td>
</tr>
<tr>
<td>ERATO11</td>
<td>630</td>
<td>Permanent AF</td>
<td>400 mg twice daily</td>
<td>Placebo</td>
<td>Ventricular rate at 2 wk</td>
<td>24-h mean ventricular rate at 2 wk decreased by 11.7 bpm; more effect with exercise</td>
<td></td>
</tr>
<tr>
<td>ANDROMEDA15</td>
<td>617</td>
<td>Recent decompensated heart failure</td>
<td>400 mg twice daily</td>
<td>Placebo</td>
<td>All-cause mortality or heart failure hospitalization</td>
<td>Increased mortality early in trial (8.1% vs 3.8%; HR=2.13)</td>
<td>Premature termination by Data Safety Monitoring Board</td>
</tr>
<tr>
<td>ATHENA12,13</td>
<td>4628</td>
<td>AF with risk factors</td>
<td>400 mg twice daily</td>
<td>Placebo</td>
<td>Cardiovascular hospitalizations and death</td>
<td>Decreased all-cause mortality or cardiovascular hospitalization (HR=0.76)</td>
<td>Stroke, AF hospitalization also reduced</td>
</tr>
<tr>
<td>DIONYSOS13</td>
<td>504</td>
<td>AF needing therapy</td>
<td>400 mg twice daily</td>
<td>Amiodarone</td>
<td>Time to first AF or drug discontinuation</td>
<td>More AF recurrence with dronedarone (63.5% vs 42%); more drug intolerance with amiodarone (13.3% vs 10.0%)</td>
<td></td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CV, cardioversion; HR, hazard ratio.
nance of Sinus Rhythm (EURIDIS and ADONIS)\textsuperscript{10} enrolled 828 patients who received 400 mg dronedarone twice daily and 409 patients who received placebo. Patients were in sinus rhythm at the time of random assignment. Patients were followed with frequent office visits and transtelephonic monitoring. For the 2 trials combined, median times to recurrence of atrial fibrillation were 116 days in the dronedarone group and 53 days in the placebo group. At 12 months, 64% of the dronedarone patients and 75% of the placebo patients had a recurrence (hazard ratio, 0.75; 95% CI, 0.55 to 0.97; \(P<0.001\)). As in DAFNE, dronedarone therapy was associated with a decrease in ventricular rate, compared with placebo, at the time of an atrial fibrillation recurrence (103±26 beats per minute versus 110±30 bpm; \(P<0.001\)).

The effects of dronedarone on heart rate in patients with permanent atrial fibrillation was studied in the Efficacy and Safety of Dronedarone for the Control of Ventricular Rate During Atrial Fibrillation Study (ERATO).\textsuperscript{11} One hundred seventy-four patients were randomly assigned between dronedarone 400 mg twice daily and placebo. Concomitant AV nodal blocking agents were permitted but were maintained constant through the study. Heart rate was assessed with serial ambulatory ECG recordings. Dronedarone slowed ventricular rates both at rest and during exercise, with a mean reduction over 24 hours of 11 bpm.

The safety of dronedarone was questioned after results of a trial of patients with recently decompensated health failure were published (see below). To better evaluate long-term safety, a very large outcomes trial in patients with atrial fibrillation (ATHENA)\textsuperscript{12,13} was conducted. Patients were over 65 years, and 47% were women. Hypertension was present in 60%. However, heart failure with severe left ventricular dysfunction was uncommon, with only 3.9% of the group having a left ventricular ejection fraction of <35% and only 4.4% having a history of class III or higher heart failure. In ATHENA, 731 of 2301 (34%) dronedarone patients had a primary outcome event, cardiovascular hospitalization (675; 29.3%), or death (59; 2.6%). In the placebo group, 917 of 2327 (39.4%) had primary outcome events, cardiovascular hospitalization (859; 36.9%), or deaths (58; 2.5%). The hazard ratio for the primary outcome, cardiovascular hospitalization or death, was 0.76 (95% CI, 0.69 to 0.84; \(P<0.001\)). Additional observations included reductions in hospitalizations for atrial fibrillation (14.6% versus 21.9%), arrhythmic deaths (1.1% versus 2.1%), and stroke (2.0% versus 3.0%).

The DIONYSOS Trial compared the safety and efficacy of dronedarone (400 mg twice daily) and amiodarone (600 mg daily for 28 days, then 200 mg daily) in patients with atrial fibrillation.\textsuperscript{13} DIONYSOS randomly assigned 504 patients with a mean age of 64±11 years. The primary composite end point included time to first atrial fibrillation recurrence, failure to cardiovert, and premature discontinuation of the study drug due to intolerance. The incidence of the composite primary end point was 75.1% in the dronedarone group versus 58.8% in the amiodarone group (hazard ratio, 1.589; 95% CI, 1.275 to 1.980). Atrial fibrillation recurrence and cardioversion failure were more common with dronedarone (36.5% and 26.9%) than with amiodarone (24.3% and 17.7%). Discontinuation due to drug intolerance was more common with amiodarone (13.3% versus 10.0%).

Dronedarone is usually well tolerated during short- and intermediate-term administration. The frequency of selected adverse events in ATHENA is shown in Table 2. Rates of bradycardia, QT prolongation, gastrointestinal complaints, and serum creatinine rise were increased in the dronedarone group over placebo. The rates of pulmonary, endocrine, and neurological adverse events were not significantly increased by dronedarone. However, it should be remembered that many of the adverse reactions to amiodarone appear after long periods of therapy. Therefore, long-term follow-up studies will be needed to evaluate fully dronedarone’s potential for toxicity. Dronedarone is contraindicated during pregnancy because it caused fetal harm in preclinical studies.

The role of dronedarone in patients with congestive heart failure remains uncertain. The ANDROMEDA Trial\textsuperscript{14} was a double-blinded study comparing dronedarone (400 mg twice daily) and placebo in patients with recently decompensated congestive heart failure. ANDROMEDA was originally designed to enroll 1000 patients with a minimum follow-up of 12 months. Seven months after the first enrollment, however, the study was stopped by its Data Safety Monitoring Board when an increased number of deaths were noted in the dronedarone group (25/310 versus 12/317; relative risk, 2.13; 95% CI, 1.07 to 4.25, \(P<0.027\)). Patients in ANDROMEDA all had recently decompensated heart failure. In ATHENA, which excluded patients with decompensated heart failure

<table>
<thead>
<tr>
<th>Table 2. ATHENA Trial: Selected Adverse Events</th>
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<tbody>
<tr>
<td>Adverse Event</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Any adverse event</td>
</tr>
<tr>
<td>Bradycardia</td>
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<tr>
<td>QT interval prolongation</td>
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<tr>
<td>Cough</td>
</tr>
<tr>
<td>Dyspnea</td>
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<tr>
<td>Interstitial lung disease</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Abnormal LFT</td>
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<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Serum creatinine increase</td>
</tr>
<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Hyperthyroidism</td>
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</tbody>
</table>

Data are from reference 12. LFT indicates liver function test.
within the previous 4 weeks, a subgroup analysis of the patients (91 dronedarone, 109 control) with stable class III heart failure and a left ventricular ejection fraction ≤35% at enrollment showed a decrease in the risk of cardiovascular hospitalization and a trend toward a reduction in mortality rates.13 Until the role of dronedarone in patients with heart failure has been better studied, the drug should not be used in patients with patients with class IV heart failure or in patients with class II or III heart failure who have had a recent decompensation. At present, there are virtually no clinical data supporting a role for dronedarone in patients with ventricular arrhythmias, even though its pharmacological profile would suggest a potential role. Further studies in this area would be useful to clinicians.

It seems likely that dronedarone will provide a valuable addition to our therapeutic options in patients with atrial fibrillation. Dronedarone was released in the United States for use in patients with atrial fibrillation in July 2009. It has moderate efficacy and, at least during intermediate term therapy, little serious toxicity. Although it may not be as potent as amiodarone, the impressive hospitalization and mortality data from ATHENA suggest that a safe and moderately effective drug can favorably affect important patient outcomes.

**Budiodarone**

Unlike dronedarone, budiodarone (AT1-2042), another compound that structurally resembles amiodarone, retains 2 iodine atoms in its molecular structure (Figure 1). A sec-butyl acetate side chain has been added at position 2 of the benzofuranaryl ring. This ester modification changes the compound's metabolic pathways such that budiodarone undergoes rapid degradation by plasma and tissue esterases, not by CYP3A-mediated oxidation, to an inactive compound. During in vitro studies, budiodarone has shown electrophysiological properties similar to amiodarone.15

Only limited clinical data on budiodarone are available. One study assessed twice-daily placebo or doses of 200, 400, 600, and 800 mg during sequential 2-week periods in a very small group of patients with paroxysmal atrial fibrillation and implanted pacemakers.16 Atrial fibrillation burden (defined as percent time in atrial fibrillation) was calculated during each period. Budiodarone reduced total atrial fibrillation burden by reducing the duration but not the number of atrial fibrillation episodes. Preliminary data from a similar but a larger phase 2 trial compared placebo and budiodarone (200, 400, and 600 mg twice daily) in 72 patients with pacemakers and paroxysmal atrial fibrillation.17 There were 54.4% and 75% reductions in AF burden in the 400 mg and 600 mg groups. Some patients manifested a rise in thyroid-stimulating hormone, but clinical symptoms of thyroid disease did not appear. There are as yet no published data on long-term exposure to budiodarone, so its potential for chronic toxicity is unknown.

**Celivarone**

Celivarone (SSR149744C) is another noniodinated benzofuran derivative (Figure 1) with electrophysiological effects similar to amiodarone.18 Few clinical data have been published in manuscript form, but a phase 2 trial tested celivarone's efficacy at 300- or 600-mg daily doses for conversion of atrial fibrillation and flutter (CORYFEE, NCT00232310) and a dose ranging study compared celivarone at 50, 100, 200, or 300 mg once daily with amiodarone for maintenance of sinus rhythm (MAIA, NCT00233441) have been completed but not yet published. A preliminary report from the dose-ranging study showed the lowest rate of atrial fibrillation recurrence at the 50 mg dose with no enhanced efficacy at the higher doses.19 In another study in patients with ICDs, 2 doses of celivarone (100 and 300 mg daily) were compared with placebo over 6 months of therapy.20 A 46% reduction in the number of sustained ventricular arrhythmia episodes requiring ICD therapy was noted in the 300 mg daily group, but this reduction did not achieve statistical significance (P=0.172). Additional trials in patients with ventricular arrhythmias and ICDs are planned.

**Vernakalant**

Vernakalant is an atrial-selective, multiple ion channel blocker that is in the advanced stages of investigation for the treatment of atrial fibrillation. Both intravenous and oral forms of vernakalant have undergone clinical trials. The intravenous form has been recommended for approval by the Cardiorenal Advisory Committee of the Food and Drug Administration, but a formal letter of approval has not been issued.21 Vernakalant is an atrial repolarization-delaying agent with its major target I_{Kur}. Vernakalant also blocks I_{to} and I_{Na}, although there is little effect on I_{Kr} or I_{Ks}.22 As I_{Kur} is present in higher density in the atria, vernakalant is relatively atrial selective. The I_{Na} inhibition is rate- and voltage-dependent.23 Vernakalant has, therefore, a much greater effect in fibrillating atria than in the ventricle and is less likely to be proarrhythmic.

Vernakalant is heptatically metabolized by CYP2D6. It is not clear what effect abnormal liver function has on the metabolism of the drug. In a study of intravenous vernakalant, coadministration of CYP2D6 inhibitors did not appear to decrease clearance, and little difference was seen in maximum plasma concentrations between CYP2D6 poor and extensive metabolizers. Differences in renal function, age, sex, race, blood pressure, and heart failure status have not been shown to affect the pharmacokinetics of vernakalant.24 Vernakalant demonstrates 2-compartment elimination pharmacokinetics, and its half-life after intravenous administration is 2 to 5 hours. The oral bioavailability of vernakalant is approximately 20%. During oral therapy in the dose range of 300 to 600 mg twice daily, steady-state concentrations are achieved in 4 days.25 It remains to be seen whether CYP2D6 poor and extensive metabolizers will require different doses during chronic oral therapy.

In a phase 1 trial of intravenous vernakalant, 29 patients were randomly assigned to receive increasing doses of vernakalant or placebo. No changes in heart rate or blood pressure were seen, but there were small increases in PR interval, QRS duration, and QT interval.26 A phase 2, multicenter, randomized, double-blind trial (CRAFT) was performed in patients with atrial fibrillation to establish efficacy and safety of intravenous vernakalant.27 Fifty-six patients were randomly assigned to 1 of 2 dose regimens for the
conversion of atrial fibrillation. Patients who received a 2-mg/kg vernakalant infusion over 10 minutes followed by a 3-mg/kg infusion if normal sinus rhythm was not restored within 15 minutes had a significant difference in conversion to sinus rhythm compared with placebo (61% versus 5%; \( P < 0.0005 \)).

This led to 4 phase 3 studies, the Atrial Arrhythmia Conversion Trials 1 to 4 (ACT 1 to 4; Figure 2).\(^{26,28–30}\) ACT 1 and ACT 3 were similar in design. Patients were randomly assigned in a 2:1 ratio to receive vernakalant or placebo, and the 3-mg/kg infusion was infused first. Pooled analyses showed that the conversion rates for vernakalant and placebo were 51.5% and 3.8% (\( P < 0.0001 \)). Only patients with "recent onset" atrial fibrillation (3 hours to 7 days) showed significant changes in the rate of conversion. The median time to conversion in ACT 3 was 8 minutes, and the conversion was durable at 24 hours. Importantly, patients with heart failure were excluded from these trials. ACT 2 was designed to evaluate AF conversion in patients with postoperative AF after coronary artery bypass grafting or valve surgery. ACT 2 showed similar rates of conversion as ACT 1 and 3. In ACT 2, none of the 10 patients with atrial flutter converted to normal rhythm, indicating this drug may not be effective for atrial flutter. A small study in atrial flutter–only patients further confirmed that vernakalant is not effective for atrial flutter.\(^{26}\)

ACT 4 was designed to further assess the safety of intravenous vernakalant. The cumulative phase 3 clinical data showed that the most common side effects were dysgeusia, sneezing, paresthesias, nausea, and hypotension (Table 3). There were documented increases in the QT interval and QRS duration, but the incidence of ventricular arrhythmias was not different between the vernakalant and placebo groups. Three cases of torsades de pointes were documented in the vernakalant group, but 2 of them occurred more than 15 days after administration of the drug and the other occurred after ibutilide was subsequently administered.

Phase 3 trials have not been completed for oral vernakalant, although phase 2 trials have been promising for the long-term maintenance of sinus rhythm.\(^{31}\) The phase 2a trial was double-blinded, randomized, and compared a 300-mg dosage, a 600-mg dosage, and placebo for 25 days after cardioversion. Electrical cardioversion was permitted for patients who did not convert within 3 days after initiation of the medication. Significantly more patients remained in sinus rhythm at the end of the trial period in the 300-mg dosing group and in the combined 300- and 600-mg groups, when compared with placebo. The phase 2b trial compared 150-, 300-, and 500-mg dosages with placebo, and the trial duration was 90 days. The 500-mg dosage group showed durable maintenance of sinus rhythm at 90 days compared with placebo, with low incidence of side effects. There were no reported cases of torsades de pointes.

In summary, intravenous vernakalant for cardioversion of recent onset AF is moderately effective for rapid termination of atrial fibrillation with durable maintenance of sinus rhythm up to 24 hours. The side effect profile shows relatively modest potential for toxicity. Age, sex, ethnicity, and concomitant illnesses do not appear to alter efficacy. Of course, drugs used only for the acute conversion of atrial fibrillation must also be compared with electrical cardioversion as well as other agents. Oral vernakalant may prove useful for maintenance of sinus rhythm, but phase 3 trials have yet to be completed. If these trials show efficacy, vernakalant probably will be more widely used in conversion attempts as a step to long-term therapy. There are no clinical data on the effects of vernakalant in ventricular arrhythmias, and its mechanisms of action suggest it would not be useful.

**Ranolazine**

Ranolazine is currently approved for the treatment of chronic angina pectoris. Ranolazine reduces myocardial ischemia by its effects on the late inward Na\(^+\) current (I\(_{\text{Na,L}}\)).\(^{32}\) During myocardial ischemia and heart failure, I\(_{\text{Na,L}}\) is augmented. This results in increased sodium entry and, via sodium-calcium exchange, increased cytosolic calcium concentra-

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**Table 3. Most Common Adverse Events With Intravenous Vernakalant**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Vernakalant (n=773), n (%)</th>
<th>Placebo (n=335), n (%)</th>
<th>( P ) Value</th>
<th>Median Time to Onset, min</th>
<th>Median Duration, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>158 (20.4)</td>
<td>8 (2.4)</td>
<td>&lt;0.0001</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Sneezing</td>
<td>116 (15.0)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>68 (8.8)</td>
<td>5 (1.5)</td>
<td>&lt;0.0001</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>50 (6.5)</td>
<td>4 (1.2)</td>
<td>&lt;0.0001</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>Hypotension</td>
<td>45 (5.8)</td>
<td>12 (3.6)</td>
<td>&lt;0.0001</td>
<td>34</td>
<td>20</td>
</tr>
</tbody>
</table>

Data are from references 28–31.
Ranolazine is an inactivated sodium channel blocker.\textsuperscript{33,34} At concentrations near its therapeutic range for angina (2 to 6 μmol/L, IC\textsubscript{50} ≈ 6 μmol/L), ranolazine inhibits I\textsubscript{Na}. In the same concentration range, ranolazine inhibits peak I\textsubscript{Na} in the atrium but not the ventricle.\textsuperscript{33,35} This effect results in reduced atrial excitability and a rate-dependent increase in postpolarization atrial refractoriness. Ranolazine also inhibits I\textsubscript{Kr} but with a higher IC\textsubscript{50} ≈ 12 μmol/L. In experiments using an isolated canine ventricular wedge preparation, ranolazine results in either no change or a decrease in transmural ventricular dispersion of refractoriness and does not produce early afterdepolarizations, triggered activity, or polymorphic ventricular tachycardia.\textsuperscript{33} In other experiments, ranolazine has been shown to suppress excitability and triggered activity in an isolated canine pulmonary vein sleeve preparation, terminate acetylcholine- and isoproterenol-induced atrial fibrillation, and prevent its reinitiation.\textsuperscript{34,36}

Ranolazine has variable systemic availability after oral administration due to its extensive first-pass metabolism in the gut and liver. Metabolism is mainly via CYP3A4 and, to a lesser extent, CYP2D6. The terminal elimination half-life is 7 hours. The recommended dosage in patients with angina is 500 to 1000 mg twice daily. Ranolazine should not be used as concurrent therapy with strong CYP3A4 inhibitors (eg, ketoconazole), and dose reduction is recommended with moderate CYP3A4 inhibitors (eg, diltiazem) or P-glycoprotein inhibitors. Ranolazine is a weak inhibitor of CYP2D6 and a moderate inhibitor of CYP2D6 and P-glycoprotein.\textsuperscript{37}

Ranolazine’s effects on ECG intervals underwent extensive study during its development for its current indication of chronic angina. Ranolazine results in a 2- to 6-ms mean increase in the QT interval, but drug-induced polymorphic ventricular tachycardia has not been observed. The MERLIN-TIMI 36 trial enrolled 6560 patients with a non–ST-elevation acute coronary syndrome who were randomly assigned to either ranolazine (intravenous initiation, then 1000 mg twice daily) or matched placebo, in addition to standard medical therapy.\textsuperscript{38} No significant improvement was shown in the primary end point of death and recurrent ischemic events with ranolazine in MERLIN-TIMI 36, but data from continuous ambulatory ECG recordings during the first 7 days of therapy were recently reported. Significant decreases in the frequency of nonsustained ventricular and supraventricular tachycardia were noted. A trend toward less frequent new-onset atrial fibrillation was also seen. A single case report on the successful use of ranolazine to suppress high-density ventricular tachycardia has been reported.\textsuperscript{39} An uncontrolled case series has also described control of recurrent atrial fibrillation in 4 of 7 patients with drug-resistant arrhythmia.\textsuperscript{40} Controlled trials with ranolazine as an antiarrhythmic drug in patients with atrial fibrillation are in the planning stages.

One form of the long-QT syndrome (LQT3) is caused by mutations in the SCN5A sodium channel that lead to enhanced and sustained activity of late I\textsubscript{Na}. Moss et al\textsuperscript{41} administered intravenous ranolazine to 5 patients with LQT3. During the infusion, ranolazine shortened QTc by 26±3 ms. Diastolic function on echocardiography was also improved.

Ranolazine may also prove useful in another form of the long-QT syndrome. The Timothy syndrome (LQT8) is a multisystem disorder characterized by facial dysmorphism, syndactyly, QT prolongation, and premature sudden death.\textsuperscript{42} The syndrome is caused by a missense mutation in Ca\textsubscript{v}1.2, the gene that encodes the α-subunit of the L-type calcium channel, resulting in a gain in function of the L-type calcium channel. In an animal model of the Timothy syndrome, ranolazine suppressed polymorphic ventricular tachycardia induced by the calcium channel agonist BayK8644.\textsuperscript{40} Clinical data on the chronic treatment of arrhythmias in LQT3 and Timothy syndrome patients are not available.

At present, the only approved indication for ranolazine is the treatment of angina. It remains to be proven whether it will also be useful as an antiarrhythmic agent.

**Ivabradine**

Ivabradine selectively inhibits the spontaneous pacemaker activity of the sinus node by blocking the I\textsubscript{f} current.\textsuperscript{43} This reduces the heart rate without altering myocardial contractility or other hemodynamics.\textsuperscript{44} Ivabradine has been approved for use as an antianginal in Europe.\textsuperscript{45} It has also been used off-label in Europe as a treatment for inappropriate sinus tachycardia. It has not yet been approved for any use in the United States. The blockage of the I\textsubscript{f} current is dose-dependent and heart rate–dependent. There is a greater efficiency in blocking I\textsubscript{f} at faster heart rates, limiting the risks of symptomatic bradycardia.\textsuperscript{46} Electrophysiological studies of ivabradine in humans have shown little effect on the conduction system or on atrial and ventricular refractoriness.\textsuperscript{47} Some remodeling of the sinus node appears to occur in response to ivabradine, but no rebound tachycardia has been seen after discontinuing the drug.\textsuperscript{48}

Ivabradine is 80% hepatically metabolized by the CYP3A4 enzyme and cannot be used concomitantly with drugs that inhibit this enzyme, such as azoles and macrolide antibiotics.\textsuperscript{49} There does not appear to be a difference in heart rate response between patients who are CYP3A4 rapid metabolizers and those who are slow metabolizers. It is 20% renally cleared. The oral bioavailability is approximately 40% and it takes 60 to 90 minutes to reach maximal plasma concentrations. The half-life is approximately 2 hours.

The major trial that evaluated ivabradine is the BEAUTIFUL study.\textsuperscript{50} This randomized, double-blind, placebo-controlled trial enrolled 10 917 patients with ischemic cardiomyopathy to receive ivabradine versus placebo. There was no difference in the primary end point of cardiovascular death or admissions for acute infarction or heart failure. In patients with baseline heart rates > 70 bpm, however, the secondary end points of admission for fatal and nonfatal infarction and the need for revascularization were significantly reduced. The heart rate reduction due to ivabradine was 6±2 bpm. A previous study compared ivabradine with atenolol for treatment of patients with stable angina and found that ivabradine was as effective as atenolol.\textsuperscript{51} It is on this basis that it was approved for use in Europe.

Composite data from phase 2 and phase 3 trials suggest that most side effects are dose-related. Ion channels in the retina that generate the I\textsubscript{h} current are also affected by...
Table 4. Upstream Therapies for the Treatment of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Clinical Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Reduced production of angiotensin II</td>
<td>Reduction in the incidence AF for patients with LV dysfunction(^66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduction in the incidence AF for post-MI patients with LV dysfunction(^67)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Angiotensin I receptor antagonist</td>
<td>Reduction in the incidence of AF for patients with LV dysfunction(^66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No reduction in recurrent AF(^68)</td>
</tr>
<tr>
<td>Statins</td>
<td>HMG-CoA reductase inhibitor, antioxidant, anti-inflammatory</td>
<td>Reduction in the incidence of AF(^69)</td>
</tr>
<tr>
<td>w-3 Polyunsaturated fatty acids</td>
<td>Lipid lowering, antiarrhythmic, antioxidant, anti-inflammatory</td>
<td>Reduction in postoperative AF(^70)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Anti-inflammatory</td>
<td>Reduction in recurrent and permanent AF(^71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduction in postoperative AF(^72)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldosterone antagonist</td>
<td>None</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>Unknown (anti-inflammatory?)</td>
<td>None</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; LV, left ventricular; MI, myocardial infarction.

ivabradine. This is the mechanism for ivabradine’s major side effect, visual luminous phenomena, also known as phosphores (14.5%). Phosphores usually resolve with continued treatment and are a rare cause of drug discontinuation. Severe bradycardia is seen in 3.3% of patients. Other less common side effects include palpitations, nausea, headaches, vertigo, muscle cramps, hypereosinophilia, and hyperuricemia.

Little trial data exists regarding the treatment of atrial tachyarrhythmias with ivabradine. The mechanism of action suggests that ivabradine may benefit patients with inappropriate sinus tachycardia. In Europe, where the drug is being marketed, it is used off-label in the treatment of inappropriate sinus tachycardia. Further data will be needed as to its effectiveness in treating this condition.

Adenosine A\(_1\) Receptor Agonists

Adenosine is frequently used for termination of supraventricular tachycardias (SVT). Adenosine terminates SVT in patient with AV nodal or AV reentry by stimulating the A\(_1\) adenosine receptor to produce transient AV block. However, adenosine induces atrial fibrillation in up to 15% of patients by decreasing the refractory period of the atrium. In addition, adenosine also stimulates the A\(_2A\), A\(_2B\), and A\(_3\) adenosine receptor subtypes, which contribute to its adverse effect profile. Stimulation of these receptors leads to a variety of systemic side effects, including flushing (18%), dyspnea (12%), and chest pain (7%). Efforts have been made to identify A\(_1\) receptor–selective agonists for both the early stages of evaluation for treatment of atrial fibrillation. Several are under investigation currently, including tecadenoson, selodenoson, and PJ-875. Tecadenoson is the furthest along in the development process. A phase 3 trial has been completed evaluating tecadenoson for the termination of SVT, and preclinical data are promising for rate control of atrial fibrillation. Selodenoson and PJ-875 are both in the early stages of evaluation for treatment of atrial fibrillation.

Preclinical studies indicate that tecadenoson is a potent and selective agonist of the A\(_1\) receptor. Studies in animal models showed that it caused significant prolongation of AV nodal conduction and refractoriness without causing hypotension or negative inotropic effects. In addition, those effects were dose-dependent and persistent with chronic administration of the drug. A phase 1 dose-escalation trial in 32 patients showed a dose-dependent prolongation of the AH interval. There was no effect on the HV interval. The peak effect on AH interval was at 1 minute, and resolution occurred at 20 minutes. Four patients had significant heart block and 3 patients had atrial fibrillation (2 after atrial pacing). Two patients had neurological effects. There is incomplete published information regarding the pharmacokinetics tecadenoson. It appears to follow a 2-compartment model and has a longer half-life than adenosine (20 to 30 minutes).

The most significant trial to evaluate tecadenoson to date is the phase 3 TEMPEST trial. This study was a multicenter, double-blinded, placebo-controlled trial that randomly assigned 181 patients to receive placebo versus 1 of several dose-escalating regimens of tecadenoson for termination of SVT. Overall, the conversion rates were 73.5% in the tecadenoson-treated patients and 6.7% in the placebo group. The rates of conversion did improve with dose escalation. Side effects were relatively mild and increased with dose escalation. Twelve patients had second-degree heart block. Two patients had complete heart block, and both of those patients were in the highest dose treatment group. Five patients in the 2 highest dose treatment groups developed transient atrial fibrillation or atrial flutter. The rates of flushing, dyspnea, and chest pain were 4%, 2.6%, and 3%, respectively. No patients in this study had alterations in blood pressure.

Table 5. Future Targets for Novel Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific acetylcholine-regulated (K^+) current inhibition(^74,75)</td>
<td></td>
</tr>
<tr>
<td>Abnormal calcium handling(^76,77)</td>
<td></td>
</tr>
<tr>
<td>Gap junction modification(^78)</td>
<td></td>
</tr>
<tr>
<td>Na (^+/Ca(^{2+}) exchange inhibition(^79)</td>
<td></td>
</tr>
<tr>
<td>Stretch-induced or ischemia-induced ATP-sensitive (K^+) current inhibitors(^80)</td>
<td></td>
</tr>
<tr>
<td>Gene and cellular therapy(^81)</td>
<td></td>
</tr>
</tbody>
</table>
An animal study of tecadenoson for rate control of atrial fibrillation has shown promising results.62 In combination with metoprolol, rate control was improved with tecadenoson compared with either agent alone. Improved rate control was seen with exercise and with rest. A phase 2 clinical trial to evaluate the safety of tecadenoson to treat atrial fibrillation has been completed.45 Results have not yet been released.

In summary, the available data regarding adenosine A1 receptor agonists, particularly tecadenoson, is promising for the conversion of SVT and for short-term rate-control of atrial fibrillation. The rate of conversion for SVT is similar to that of adenosine, but the systemic side effects are milder. In addition, although adenosine A1 receptor stimulation is the presumed mechanism for the induction of atrial fibrillation, tecadenoson appears less likely to cause atrial fibrillation, perhaps because the maximal action potential shortening seen with a bolus of adenosine is not observed with longer-acting agents.

**Upstream Therapy**

It is now recognized that atrial fibrillation originates from atrial tissue that has altered structure or function. Fibrosis within the atrium is 1 of the major mechanisms of atrial remodeling, which provides the substrate for atrial fibrillation generation and maintenance.54 Efforts have been made to develop "upstream" therapies for atrial fibrillation, and some preliminary examples are listed in Table 4.65 The renin-angiotensin-aldosterone system has been implicated in the fibrotic process. Therapies that alter renin-angiotensin-aldosterone system, as well as antiinflammatory and antioxidative drugs, are being investigated both alone and in combination with traditional antiarrhythmic drugs. For some newer drugs, data have only been generated in animal models. Further studies will be needed to delineate the full potential benefits of these and other therapies.

**Future Targets for Antiarrhythmic Drugs**

Additional approaches to antiarrhythmic therapy continue to be explored, and some examples are listed in Table 5. It is probable that novel agents directed at these targets will enter clinical trials in the next several years. If these efforts prove successful, drug therapy may reemerge as an equal partner to ablation and device approaches in the treatment of patients with arrhythmias.

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**References**

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