Antiarhythmic medications have been available for nearly 100 years and remain a mainstay in the management of atrial fibrillation (AF). Goals of therapy with the use of these drugs include a reduction in the frequency and duration of episodes of arrhythmia as well as an emerging goal of reducing mortality and hospitalizations associated with AF. The use of these drugs has been limited by both proarrhythmic and noncardiovascular toxicities as well as often modest antiaarrhythmic efficacy. Despite these limitations, antiarrhythmic drugs remain widely prescribed for the management of symptomatic AF, and a host of new antiarrhythmic drugs are in various stages of clinical development. This review will focus primarily on antiarrhythmic drug use in patients with AF in the absence of significant structural heart disease or congestive heart failure.

The Decision to Maintain Sinus Rhythm
A multitude of studies have evaluated the health-related outcomes associated with a strategy of rate compared with rhythm control in patients with AF. These studies, which included primarily patients aged ≥60 years with at least 1 risk factor for stroke, failed to demonstrate a mortality benefit associated with a rhythm control strategy. This equivalence in outcome was in part related to toxicities associated with antiarrhythmic drug therapy as well as excess stroke risk in patients in whom anticoagulation was discontinued. Important groups of patients, including younger individuals without thromboembolic risk factors and the elderly (≥80 years), were excluded from these trials, but the results were nonetheless applicable to a large percentage of the AF population. As a likely consequence of these landmark studies, rates of AF-associated hospitalization, cardioversion, and antiarrhythmic drug use plateaued or fell in the years after their publication.

Currently Available Antiarrhythmic Drugs
Antiarrhythmic drugs do not lend themselves to a neat classification scheme. Many of these drugs have effects on multiple ion channels and adrenergic receptors as well as a myriad of cardiac and noncardiovascular side effects. The majority of available antiarrhythmic drugs exert predominant effects on cardiac sodium or potassium currents. The sodium channel blocking drugs are often called membrane-stabilizing agents because they decrease the excitability of cardiac tissue. Quinidine and disopyramide have intermediate sodium channel blocking activity and exhibit use dependence. This means that the predominant effect on conduction (sodium channel blockade) is seen at rapid heart rates. In fact, these agents largely affect potassium channels ($I_{K}$) at normal or slow heart rates and low concentrations and therefore display “reverse use dependence” for potassium channel blockade. Procainamide and flecainide have the slowest dissociation kinetics of the sodium channel blocking drugs and therefore have more bound drug and produce a greater degree of conduction slowing at rapid heart rates (use dependence).

Drugs with significant effects on potassium currents prolong the action potential duration and refractory periods. Sotalol and dofetilide are potassium channel blocking drugs that display reverse use dependence such that repolarization is prolonged at slow heart rates. Amiodarone and dronedarone affect a broad range of channels including sodium, calcium, and multiple potassium channels.

Quinidine derives from the bark of the cinchona plant and was identified as a potential antiarrhythmic drug a century ago (Tables 1 and 2). It is a vagolytic and $\alpha$ blocking agent with an intermediate sodium channel blocking effect at rapid heart rates and higher concentrations and a potassium channel blocking effect at slower heart rates and normal concentrations. It is rarely used for AF; however, its blocking effect on $I_{K}$ has generated interest as a potential therapy for Brugada syndrome. 

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Atrial Fibrillation

Antiarrhythmic Drug Therapy for Atrial Fibrillation

Peter Zimetbaum, MD
syndrome and idiopathic ventricular fibrillation. Its noncardiovascular side effects include diarrhea as well as cinchonism (tinnitus and headache) and thrombocytopenia. The addition of verapamil to suppress quinidine-associated early afterdepolarizations may reduce the risk of torsades de pointes (TDP) associated with quinidine use.

Disopyramide is distinguished as a sodium channel blocking drug with potent anticholinergic and negative inotropic effects. The anticholinergic effects have led to its recommendation for patients with vagally induced AF despite little supporting evidence. The negative inotropic effects of this drug make it a viable therapy for patients with AF and hypertrophic cardiomyopathy. It should be avoided in the setting of narrow-angle glaucoma, prostatic hypertrophy, or myasthenia gravis. Disopyramide prescriptions represent 1% to 2% of annual antiarrhythmic drug prescriptions in the United States.

Flecainide and propafenone are recommended for the management of patients with AF without structural heart disease. They are contraindicated in individuals with prior myocardial infarction and reduced left ventricular function because of a risk of ventricular proarrhythmia. At present, they each represent 10% of annual US antiarrhythmic drug prescriptions. Flecainide, in addition to significant sodium channel blocking activity, has mild IKr blocking effects but is not generally associated with significant QT prolongation. It has mild negative inotropic effects and, like propafenone, is associated with a significant incidence of atrial flutter. Dizziness and visual disturbance represent the common noncardiovascular side effects seen in 5% to 10% of patients taking flecainide. Propafenone has β blocking in addition to sodium channel blocking activity. It also has mild negative inotropic and chronotropic effects. The major noncardiovascular adverse effects include a metallic taste as well as dizziness and visual disturbances.

Sotalol is a potassium channel (IKr) blocker and β-blocker with minimal noncardiovascular side effects and a high rate of utilization (26% of annual prescriptions in the United States). It is renally cleared and is prescribed twice daily unless the creatinine clearance is between 30 and 60 mL/min, in which case it should be dosed daily. The usual dose range is 160 to 480 mg/d in divided dosages. It is generally started at a dose of 80 mg twice daily and uptitrated with attention to QT prolongation. The potassium channel blocking effect increases with increasing dosage, and, as a result, the risk of ventricular proarrhythmia (TDP) increases at a higher dosage.

Dofetilide is also an IKr blocker but without other clinically significant electrophysiological effects. It is renally cleared and must be dosed according to creatinine clearance (Tables 1 and 2). It was approved for use in the United States in 2000 with a 3-day mandatory in-hospital loading period and currently represents $2% of antiarrhythmic drug prescriptions annually. Dofetilide is more effective for the maintenance of sinus rhythm than it is for restoring sinus rhythm. It has been demonstrated to be reasonably safe in heart failure and post–myocardial infarction populations.

Amiodarone, although not approved by the Food and Drug Administration for AF, is the most commonly prescribed antiarrhythmic drug for AF, representing 45% of annual drug prescriptions. It is a complex iodinated compound that, along with its active metabolite N-desethylamiodarone, blocks IKr, IKur, INa, IKs, ICa,L, IKCa,L, and If channels with noncompetitive antagonism of α- and β-receptors. It is distinguished by a half-life of weeks and significant distribution into adipose tissue. It is the most effective antiarrhythmic drug currently available but is limited by a myriad of noncardiovascular side effects (Table 1). The major cardiovascular side effect of amiodarone is sinus bradycardia, with a higher risk of pacemaker requirement in women. QT prolongation is common but very rarely associated with TDP (<0.5%). It should be loaded (600–1200 mg/d) for a total of 10 g over 10 days to 4 weeks before being reduced to a maintenance dose of 100 to 200 mg/d. Administration in divided doses and with food minimizes the gastrointestinal symptoms associated with its use. Administration with food is also recommended because it significantly increases the rate and extent of amiodarone absorption. The combination of amiodarone with the CYP3A4 substrate simvastatin has been associated
with an increased risk of myositis⁵ (Table 3). Conversely, this risk seems to be smaller when amiodarone is combined with pravastatin, which does not use the cytochrome P450 system for metabolism. The most important interaction of amiodarone occurs with the potentiation of the anticoagulant effect of warfarin through inhibition of CYP2C9. In addition, amiodarone inhibits P-glycoprotein transport and can reduce digoxin clearance.

Amiodarone requires surveillance for liver, lung, and thyroid toxicity.²¹ Hepatic toxicity is manifest as low-level transaminase elevation, which, if not detected and managed with discontinuation of amiodarone, can result in cirrhosis. Pulmonary toxicity can manifest as an acute hypersensitivity type of reaction with patchy infiltrates after weeks of therapy or as a more chronic process with interstitial fibrosis. Adult respiratory distress syndrome and solitary pulmonary nodules have also been described as manifestations of amiodarone therapy.²⁶ The recognition of pulmonary toxicity requires a high index of suspicion with attentiveness to complaints of cough and dyspnea. The diagnosis remains one of exclusion, but high-resolution computed tomographic scan or histopathological demonstration of intra-alveolar foamy macrophages with cytoplasmic lamellar inclusions in bronchial washings can be helpful.²⁷ Amiodarone inhibits the conversion of T4 to T3, and an elevated thyrotropin is expected in the initial months of therapy. Hypothyroidism should not be
Therapies in Development

Most new antiarrhythmic medications are formulated with the intent of reducing proarrhythmic toxicity. Vernakalant is one such new multichannel blocking antiarrhythmic drug. It acts predominantly on the atrial potassium currents ($I_{\text{pot}}$, $I_{\text{Ach}}$, $I_{\text{Kad}}$) with a use- or rate-dependent effect on cardiac sodium channels, including the late sodium current $I_{\text{sat}}$. It appears to be far more effective for the conversion of AF than atrial flutter, particularly if administered within 7 days of arrhythmia onset. Multiple studies to date have demonstrated no significant proarrhythmia. The intravenous formulation is under investigation in the United States but has been approved in Europe. The oral formulation is in clinical development. The major side effects of vernakalant include cough, sneezing, and dysgeusia.

Budiodarone is another structural analogue of amiodarone with similar multichannel blocking properties. It is an iodin-
ated compound but is metabolized by plasma and tissue esterases rather than the CYP3A4 system. This difference allows more rapid metabolism and a lower likelihood of side effects. This agent has been evaluated in a study of patients with paroxysmal atrial fibrillation and pacemakers. The continuous monitoring afforded by pacemakers allows a true determination of recurrence not fully reflected in most anti-arrhythmic drug studies. In this study, the duration and frequency of recurrent AF episodes were diminished.

Ranolazine is a new drug approved for the management of chronic angina. It blocks a number of currents including peak and late INa, ICaL, and IKr. Preliminary clinical data with the use of ranolazine as an anti-ischemic drug have demonstrated a reduction in supraventricular arrhythmias including AF. Experimental data have demonstrated the synergistic potential for the combination of ranolazine with amiodarone or dronedarone to reduce the development of and facilitate the termination of AF. In addition, it is postulated that the late sodium current contributes to the prolongation of the action potential duration associated with reduced IKr at slow heart rates. Inhibition of INa with ranolazine or vernakalant may reduce the risk of TDP associated with IKr inhibition. It remains to be determined whether combination therapy with ranolazine or vernakalant and IKr blockers such as sotalol, quinidine, or dofetilide will reduce the risk of TDP.

Proarrhythmic Toxicity of Antiarrhythmic Drugs

Sodium channel blocking drugs slow conduction and, in susceptible patients with preexisting scar or ischemia, can promote the development of reentry and ventricular tachyarrhythmias. As noted, atrial flutter is a common arrhythmia in patients treated with sodium channel blocking drugs for AF. Typically, the atrial rate is much slower than 300 bpm and can result in 1:1 atrioventricular conduction with a wide QRS morphology due to slowed conduction (Figure). This accelerated ventricular rate accompanied by prolonged conduction can result in hemodynamic collapse. For this reason, many clinicians choose to use atrioventricular nodal blocking drugs with flecainide and propafenone. We routinely evaluate QRS duration after initiation of sodium channel blocking drugs with exercise to test the use-dependent properties of this drug. It is our practice (without supporting data) to reduce the dose or discontinue the therapy if the QRS duration exceeds 125% of the baseline value. Sodium channel blocking drugs can also present a risk of proarrhythmia in patients with loss-of-function sodium channel mutations such as some patients with Brugada syndrome. These abnormalities in sodium channel function may influence the degree of conduction slowing or transmural voltage gradient (ST elevation in the right precordial leads), which may predispose to ventricular proarrhythmia. Quinidine, because of its effects on IKr, does not exacerbate the ST elevation that may be seen with other sodium channel blocking drugs. It is our practice to discontinue sodium channel blocking drugs in patients who develop precordial ST elevation.

Drugs with potassium channel blocking activity carry a risk of TDP. In most instances, this occurs through reduction in the potassium current IKr. This complication is most commonly seen at slow heart rates, particularly after a pause with conversion of AF to sinus rhythm. Hypokalemia, hypomagnesemia, female gender, baseline prolonged QT interval, or congenital long-QT syndrome and concomitant use of other QT-prolonging therapies are all risk factors for TDP. The risk of QT prolongation and TDP is dose related.
Table 4. Recommendations for Antiarrhythmic Drug Use

<table>
<thead>
<tr>
<th>Severe Ventricular Hypertrophy (hypertrophic cardiomyopathy)</th>
<th>First line</th>
<th>Second line</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Structural Heart Disease</td>
<td>Coronary Artery Disease</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>No Structural Heart Disease</td>
<td>Amiodarone</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>No Structural Heart Disease</td>
<td>Propafenone</td>
<td>Sotalol</td>
</tr>
<tr>
<td>No Structural Heart Disease</td>
<td>Dronedarone</td>
<td>Dronedarone</td>
</tr>
<tr>
<td>No Structural Heart Disease</td>
<td>Sotalol</td>
<td>Dofetilide</td>
</tr>
<tr>
<td>No Structural Heart Disease</td>
<td>Amiodarone</td>
<td>Disopyramide</td>
</tr>
<tr>
<td>No Structural Heart Disease</td>
<td>Propafenone, sotalol</td>
<td></td>
</tr>
<tr>
<td>No Structural Heart Disease</td>
<td>Propafenone, sotalol</td>
<td></td>
</tr>
<tr>
<td>No Structural Heart Disease</td>
<td>Propafenone, sotalol, dronedarone</td>
<td></td>
</tr>
</tbody>
</table>

with sotalol and dofetilide but not with quinidine or disopyramide. QT prolongation is an expected finding with amiodarone but is very rarely associated with proarrrhythmia. Ventricular hypertrophy may predispose to the development of afterdepolarizations and thus may represent a substrate more prone to TDP in the presence of QT-prolonging medications (potassium channel blocking drugs).49

**Drug Selection and Comparative Efficacy of Drugs for Maintaining Sinus Rhythm**

The clinical use of these drugs for AF is guided first by the risk of toxicity and then by efficacy (Table 4). Recently published guidelines for drug selection in patients with AF from both the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society and European Society of Cardiology agree on the use of flecainide, propafenone, sotalol, dronedarone, or amiodarone in patients without significant underlying heart disease (ie, heart failure, coronary artery disease, or severe left ventricular hypertrophy).9,50 The European guidelines suggest that disopyramide be considered for patients with a vagal trigger associated with AF, whereas quinidine, procainamide, and disopyramide are completely omitted from the US guidelines. Dofetilide is not approved for use in Europe but is indicated in all clinical categories in the US guidelines. Both guidelines agree on the use of sotalol, amiodarone, and dronedarone for patients with coronary artery disease and amiodarone for patients with symptomatic congestive heart failure. Patients with left ventricular hypertrophy have the same drug choices as those without structural heart disease; however, severe left ventricular hypertrophy is considered a risk for toxicity with most potassium and sodium channel blocking drugs. The European Society of Cardiology guidelines suggest dronedarone or amiodarone for severe left ventricular hypertrophy, whereas the US guidelines suggest only amiodarone.

Amiodarone has been directly compared with dronedarone, sotalol, and propafenone and found to be substantially more effective, with a 1-year rate of maintaining sinus rhythm of >65% (Table 5).33,34,51,52 In general, the rate of maintaining sinus rhythm is closer to 30% to 50% at 1 year for the other tested antiarrhythmic drugs.51–53 Dofetilide has also been associated with an ~50% rate of maintaining sinus rhythm at 1 year, with the greatest success in those patients who can tolerate the maximum dosage.18

Dronedarone has been compared with amiodarone in a short-duration study of comparative efficacy and safety.34 In this study, the absence of chemical cardioversion and recurrence of AF after cardioversion occurred more often with dronedarone than amiodarone (64% versus 42%). Two larger studies comparing dronedarone with placebo over a longer duration of follow-up (12 months) documented efficacy rates of ~35% for maintenance of sinus rhythm.33 A mixed treatment comparative analysis of the available antiarrhythmic drugs used in randomized controlled trials found amiodarone to be associated with the greatest rates and dronedarone with the lowest rates of sinus rhythm.33 Dronedarone was the best tolerated of the antiarrhythmic drugs, with the lowest rates of severe adverse events and a significant reduction in the risk of stroke.33,34

It is our practice to use propafenone, flecainide, sotalol, and dronedarone as first-line therapies in patients without structural heart disease (Table 4). Dofetilide and amiodarone are second choices because of the in-hospital loading requirement of the former and the risk of noncardiovascular toxicities with the latter. We occasionally choose amiodarone as a first-line therapy in elderly patients without structural heart disease for whom long-duration therapy and therefore side effects are unlikely. We choose sotalol or dronedarone as first-line therapy for patients with coronary artery disease and relatively preserved left ventricular function. If coronary artery disease is associated with left ventricular dysfunction,

Table 5. Selected Studies of Comparative Efficacy of Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients, Duration of Follow-Up</th>
<th>Drugs</th>
<th>Percentage of Patients Without Documented AF Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTAF51</td>
<td>403, 16 mo Amiodarone</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>SAFE-T52</td>
<td>665, 33 mo Amiodarone</td>
<td>65</td>
<td>Sotalol 37, Propafenone 37</td>
</tr>
<tr>
<td>PAFAC53</td>
<td>848, 9 mo Sotalol</td>
<td>33</td>
<td>Placebo 10, Dronedarone 25</td>
</tr>
<tr>
<td>DIONYSOS34</td>
<td>504, 7 mo Amiodarone</td>
<td>58</td>
<td>Quinidine plus verapamil 35</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CTAF, Canadian Trial of Atrial Fibrillation; SAFE-T, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial; PAFAC, Prevention of Atrial Fibrillation After Cardioversion; and DIONYSOS, Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation.
we choose dofetilide or amiodarone. Patients with AF and congestive heart failure are treated with dofetilide or amiodarone. In our practice, we also consider disopyramide as an option in women with preserved ventricular function and in patients with hypertrophic cardiomyopathy, particularly if they already have a pacemaker or implantable cardioverter-defibrillator.\(^\text{13}\) Our goal with the use of any antiarrhythmic drug is a reduction in the frequency of symptomatic AF. Occasional recurrences of AF on an antiarrhythmic drug are expected and do not necessarily constitute a reason to discontinue therapy if the frequency and symptoms associated with AF have been reduced significantly.

**Drugs for Cardioversion of AF**

Chemical cardioversion can be accomplished with intravenous or oral antiarrhythmic drugs. In general, the conversion success of antiarrhythmic drug therapy is significantly higher for acute (≤7 days) compared with longer-duration AF. Ibutilide is an intravenous LK channel blocker that also enhances the late inward sodium current.\(^\text{54}\) Ibutilide is \(\approx 50\%\) effective at restoring sinus rhythm. It is slightly more effective for atrial flutter than for AF.\(^\text{54}\) Patients must be monitored closely for QT prolongation and TDP for at least 2 hours after infusion.\(^\text{54}\) Amiodarone can also be used as an intravenous converting agent; however, it is weakly effective for this purpose.\(^\text{38,55}\) In the absence of conversion, intravenous amiodarone provides rate-controlling effects. Oral amiodarone can be used to convert AF to sinus rhythm. This agent can be loaded over the course of 3 to 4 weeks with a rate of conversion of \(\approx 27\%.\(^\text{52}\) Flecaainide and propafenone are available as intravenous agents in Europe but not in the United States. High-dose oral flecaainide (200–300 mg) or propafenone (450–600 mg) has been used as a “pill in the pocket” approach in patients presenting within an average of 30 minutes of arrhythmia onset. The overall rate of conversion in this study was >85\%.\(^\text{56}\) This should be restricted to patients without structural heart disease and should be first tested as a safe strategy in a monitored setting.

Vernakalant has been evaluated in a series of clinical trials for the conversion of AF.\(^\text{36,37}\) A recent study compared vernakalant with intravenous amiodarone and demonstrated a 50% rate of conversion of AF at 90 minutes with vernakalant compared with a 5% conversion rate with amiodarone.\(^\text{38}\)

**Outpatient Initiation of Antiarrhythmic Drugs**

Some controversy exists regarding the safety of the outpatient initiation of antiarrhythmic drugs. This caution primarily relates to concerns for QT prolongation and TDP, particularly at the time of conversion from AF to sinus rhythm.\(^\text{48}\) As noted, dofetilide is the primary drug for which inpatient initiation is mandated. Sotalol is also approved for AF with a recommendation for inpatient initiation. The Sotolol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) initiated either sotalol or amiodarone in the outpatient setting during AF without adverse effect and with an equivalent rate of restoring sinus rhythm. It is our practice to load all antiarrhythmic drugs other than dofetilide in the outpatient setting. We initiate these therapies once sinus rhythm has been established and monitor for proarrhythmia with scheduled daily transmissions as well as additional symptomatic transmissions using an event recorder for 10 days.\(^\text{57,58}\) We routinely load amiodarone during AF for up to a month before electric cardioversion.

**Upstream Therapies**

The concept of preventing the development of atrial electric and mechanical remodeling and thereby reducing the likelihood of AF is referred to as “upstream” therapy. Potential agents in this category include blockers of the renin-angiotensin axis, aldosterone inhibitors, polyunsaturated fatty acids, and statins.\(^\text{59}\) The angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been studied for the primary and secondary prevention of AF. There are reasonable data to support the use of angiotensin receptor blockers for the reduction of new-onset AF in patients with hypertension but without significant structural heart disease.\(^\text{60–62}\) Conversely, the benefit of these therapies in patients with congestive heart failure or multiple cardiovascular risk factors has been less robust.\(^\text{60}\) Similarly, the benefit of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for the secondary prevention of AF has not been demonstrated.\(^\text{59,60}\) At present, there are no conclusive data to support the use of aldosterone inhibitors or polyunsaturated fatty acids for the primary or secondary prevention of AF.\(^\text{59}\) Studies of statins for the primary or secondary prevention of AF have been conflicting and do not support specific antiarrhythmic recommendations.\(^\text{59,63}\) It is likely that agents in this category of upstream therapy will be most effective when administered before the development of significant atrial fibrosis.

Antiarrhythmic drugs continue to play an important role in the management of AF. A thorough understanding of the patient groups most appropriate for individual therapies is critical for the safe and effective use of these drugs. Newer approaches to antiarrhythmic drug therapy include the prevention or reversal of atrial remodeling as well as the development of conventional ion channel blocking drugs with less potential for proarrhythmia. The ultimate goal of these therapies is also likely to evolve beyond the conventional metric of time to first AF recurrence. Newer end points including AF burden, stroke risk, hospitalization, mortality, cost, and quality of life will all likely play important roles in the development of new therapies.

**Disclosures**

None.

**References**


Key Words: antiarrhythmic agents ■ antiarrhythmic drugs ■ atrial fibrillation ■ atrial fibrillation arrhythmia ■ atrial flutter
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Peter Zimetbaum

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