Antiarrhythmic 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 antiarrhythmic 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.6–9 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.6 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.7 This trend has been reversed in the latter part of this decade, with an increase in rhythm control strategies driven largely by increased rates of AF ablation and an 2%/y increase in antiarrhythmic drug prescriptions.7,8 At present, practice guidelines recommend antiarrhythmic therapy for patients with significant symptoms despite adequate rate control.9 This designation of rate control as the primary strategy for AF will likely be challenged with further advances in ablative and pharmacological therapies for AF. In addition to the aforementioned considerations, I also consider maintenance of sinus rhythm in young patients (<60 years) who have not been adequately represented in the previously cited studies and for whom the long-term implications of permanent AF are unknown. Given the recognition that leaving a patient in permanent AF will likely render future rhythm control therapies less effective, a strategy of sinus rhythm maintenance in younger patients is particularly worthwhile if one wishes to remain a candidate for developing rhythm control strategies.

**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. Propafenone 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 α 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 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. It has been demonstrated to be reasonably safe in heart failure and post–myocardial infarction populations.

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 \( \mathrm{I}_{\mathrm{Na}} \) 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 \( \beta \) 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 (\( \mathrm{I}_{\mathrm{K}} \)) blocker and \( \beta \)-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 \( \mathrm{I}_{\mathrm{Kr}} \) 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 \( \approx 2\% \) 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 \( \mathrm{I}_{\mathrm{Kr}} \), \( \mathrm{I}_{\mathrm{Na}}, \mathrm{I}_{\mathrm{Kur}}, \mathrm{I}_{\mathrm{to}}, \mathrm{I}_{\mathrm{Cal}}, \mathrm{I}_{\mathrm{Kach}}, \) and \( I_f \) channels with noncompetitive antagonism of \( \alpha \)- and \( \beta \)-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

<table>
<thead>
<tr>
<th>Antiarrhythmic Drug, Year of Development/Approval</th>
<th>Channel(s) Blocked</th>
<th>ECG Manifestations</th>
<th>Effect on Defibrillation Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine, 1918</td>
<td>( \mathrm{I}<em>{\mathrm{Na}}, \mathrm{I}</em>{\mathrm{Kr}}, \mathrm{I}<em>{\mathrm{to}}, \mathrm{I}</em>{\mathrm{Ach}}, \alpha )</td>
<td>May ( \uparrow ) sinus rate; ( \uparrow ) QT (not dose related); ( \uparrow ) PR; ( \uparrow ) QRS</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Disopyramide, 1962</td>
<td>( \mathrm{I}<em>{\mathrm{Na}}, \mathrm{I}</em>{\mathrm{Kr}}, \mathrm{I}<em>{\mathrm{to}}, \mathrm{I}</em>{\mathrm{Ach}}, \alpha )</td>
<td>May ( \uparrow ) sinus rate; ( \uparrow ) QT (not dose related); ( \uparrow ) PR; ( \uparrow ) QRS</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Propafenone, 1976</td>
<td>( \mathrm{I}_{\mathrm{Na}}, \beta )</td>
<td>May ( \downarrow ) sinus rate, ( \uparrow ) PR, ( \uparrow ) QRS</td>
<td>Varies</td>
</tr>
<tr>
<td>Flecaïnine, 1975</td>
<td>( \mathrm{I}_{\mathrm{Na}} )</td>
<td>May ( \downarrow ) sinus rate, ( \uparrow ) PR, ( \uparrow ) QRS</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Sotalol, 1992, 2000 (AF)</td>
<td>( \mathrm{I}_{\mathrm{Na}}, \beta )</td>
<td>( \downarrow ) Sinus rate, may ( \uparrow ) PR, ( \uparrow ) QT (dose related)</td>
<td>( \downarrow )</td>
</tr>
<tr>
<td>Dofetilide, 2000 (US only)</td>
<td>( \mathrm{I}_{\mathrm{Kr}} )</td>
<td>( \uparrow ) QT (dose related)</td>
<td>( \downarrow )</td>
</tr>
<tr>
<td>Ibutilide (intravenous), 1995</td>
<td>( \mathrm{I}<em>{\mathrm{Kr}}, \mathrm{I}</em>{\text{a}-\text{desethylamiodarone}} )</td>
<td>( \uparrow ) QT (dose related)</td>
<td>Not relevant</td>
</tr>
<tr>
<td>Amiodarone, 1967</td>
<td>( \mathrm{I}<em>{\mathrm{Na}}, \mathrm{I}</em>{\mathrm{Kr}}, \mathrm{I}<em>{\mathrm{cal}}, \beta, \alpha, \mathrm{I}</em>{\text{a}-\text{desethylamiodarone}} )</td>
<td>( \downarrow ) Sinus rate, ( \uparrow ) PR, ( \uparrow ) QRS, ( \uparrow ) QT</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Dronedarone, 2009</td>
<td>( \mathrm{I}<em>{\mathrm{Na}}, \mathrm{I}</em>{\mathrm{Kr}}, \beta, \alpha, \mathrm{I}_{\text{a}-\text{desethylamiodarone}} )</td>
<td>( \downarrow ) Sinus rate, ( \uparrow ) PR</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Vernakalant (intravenous), 2010 (Europe only)</td>
<td>( \mathrm{I}<em>{\mathrm{Kr}}, \mathrm{I}</em>{\text{a}-\text{desethylamiodarone}} )</td>
<td>QT prolongation</td>
<td>Not relevant</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; US, United States.

Table 1. Effects of Antiarrhythmic Drugs
with an increased risk of myositis (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. 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. 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. Amiodarone inhibits the conversion of T4 to T3, and an elevated thyrotropin is expected in the initial months of therapy. Hypothyroidism should not be
study of A Placebo-Controlled, Double-Blind, Parallel-Arm
the dronedarone-treated group.29 It is therefore contraindi-
gestive heart failure demonstrated an increased mortality in
of dronedarone on mortality in patients with advanced con-
iodine moieties. An initial study designed to assess the effect
present or persist after discontinuation of therapy because of
mortality associated with this drug.30,31 In addition, a sub-
curred in patients with decompensated congestive heart failure.
there was an increase in the serum digoxin concentration in the
dronedarone treated patients which was unlikely to be solely
responsible for the adverse outcomes. Dronedarone does not
increase the international normalized ratio in association with
warfarin use. It raises the serum creatinine level through
impaired tubular secretion without an effect on renal function.
Dronedarone, like amiodarone, interacts with the P glycopro-
tein transporting system, and digoxin should be dose reduced
or some other factor. In the Permanent Atrial Fibrillation
Outcome Study Using Dronedarone on Top of Standard
Therapy (PALLAS) dronedarone use in patients with perma-
nent atrial fibrillation was associated with an excess risk of
stroke, cardiovascular death and hospitalizations.33a There
was an increase in the serum digoxin concentration in the
dronedarone treated patients which was unlikely to be solely

Table 3. Selected Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Drug Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>↑ Digoxin and amiodarone concentrations; quinidine inhibits CYP2D6 and may increase drugs metabolized by this enzyme (eg, ↑ effect of tricyclic antidepressants, haloperidol, some β-blockers, fluoxetine, narcotics); quinidine metabolism is inhibited by cimetidine; quinidine metabolism is increased by phenobarbital, phenytoin, and rifampicin</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>None</td>
</tr>
<tr>
<td>Propafenone</td>
<td>May decrease the metabolism of warfarin; increased digoxin levels</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>May increase digoxin levels; flecaïnide levels are increased by amiodarone, haloperidol, quinidine, cimetidine, and fluoxetine</td>
</tr>
<tr>
<td>Sotalol</td>
<td>No significant interactions</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Contraindicated with verapamil, ketoconazole, cimetidine, megestrol, prochlorperazine, and thiramprimb; hydrochlorothiazide increases dofetilide levels; must discontinue amiodarone at least 3 mo before dofetilide initiation</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>None</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Inhibits CYP450 enzymes; increases concentrations of warfarin, digoxin, cyclosporine, alprazolam, carbamazepine, statins (simvastatin), phenytoin, and quinidine; increases the effect of dabigatran but does not appear to be clinically relevant</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Inhibits CYP3A4; will increase levels of alprazolam, carbamazepine, dihydropyridine, cyclosporine, statins, digoxin; verapamil (but not diltiazem) increases dronedarone levels; contraindicated in the presence of strong CYP3A4 inhibitors such as ketoconazole, itraconazole, cyclosporine, clarithromycin, and ritonavir; increases effects of dabigatran</td>
</tr>
</tbody>
</table>

diagnosed unless the free T4 is depressed. Hyperthyroidism
most often presents in the months to first few years after
initiation of therapy. Recurrent AF may be a sign when other
typical manifestations of hyperthyroidism are often absent.
Type 1 amiodarone-related hyperthyroidism frequently occurs
in the setting of a preexisting nodule or Grave’s disease.
Type 2 is a destructive thyroiditis that ultimately results in
hypothyroidism.28 The adverse effects of amiodarone can
present or persist after discontinuation of therapy because of
its long half-life.

Dronedarone is the first of a group of drugs that have been
designed to resemble amiodarone with fewer noncardiovas-
cular side effects. It is similar in structure to amiodarone with
the addition of a methylsufonamide group and absence of
iodine moieties. An initial study designed to assess the effect
of dronedarone on mortality in patients with advanced con-
gestive heart failure demonstrated an increased mortality in
the dronedarone-treated group.29 It is therefore contraindi-
cated in patients with decompensated congestive heart failure.
Subsequent efficacy studies and a major safety study in
healthier patients with AF and without decompensated heart
failure have shown no significant extracardiovascular toxic-
ities and a reduction in hospitalizations and cardiovascular
mortality associated with this drug.30,31 In addition, a sub-
study of A Placebo-Controlled, Double-Blind, Parallel-Arm
Trial to Assess the Efficacy of Dronedarone 400 mg BID for the
Prevention of Cardiovascular Hospitalization or Death
From Any Cause in Patients With Atrial Fibrillation/Atrial
Flutter (ATHENA) demonstrated a reduction in stroke asso-
ciated with dronedarone use.32 Dronedarone has been the only
antiarrhythmic drug that has demonstrated a reduction in
stroke risk in patients with AF.33 It is unclear whether this
stroke reduction was due to the maintenance of sinus rhythm
or some other factor. In the Permanent Atrial Fibrillation
Outcome Study Using Dronedarone on Top of Standard
Therapy (PALLAS) dronedarone use in patients with perma-
nent atrial fibrillation was associated with an excess risk of
stroke, cardiovascular death and hospitalizations.33a There
was an increase in the serum digoxin concentration in the
dronedarone treated patients which was unlikely to be solely

Selected Antiarrhythmic 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_{ACh}, I_{Kur})
with a use- or rate-dependent effect on cardiac sodium
channels, including the late sodium current I_{Na,L}. It appears
to be far more effective for the conversion of AF than atrial
flutter, particularly if administered within 7 days of arrhyth-
mia onset. Multiple studies to date have demonstrated no
significant proarrhythmia.36–38 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.38

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, I CaL, 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 atroventricular 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.
with sotalol and dofetilide but not with quinidine or disopyramide. QT prolongation is an expected finding with amiodarone but is very rarely associated with proarrhythmia. 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 the European Society of Cardiology agree on the use of flecainide, propafenone, sotalol, dofetilide, or amiodarone in patients without significant underlying heart disease (i.e., 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, procanamide, 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 dofetilide 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 dofetilide or amiodarone for severe left ventricular hypertrophy, whereas the US guidelines suggest only amiodarone.

Amiodarone has been directly compared with dofetilide, 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

Dofetilide 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 dofetilide than amiodarone (64% versus 42%). Two larger studies comparing dofetilide with placebo over a longer duration of follow-up (12 months) documented efficacy rates of ~35% for maintenance of sinus rhythm.30 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 dofetilide with the lowest rates of sinus rhythm.33 Dofetilide 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 dofetilide as first-line therapies in patients with AF and 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 dofetilide 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,
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.13 Our goal with the use of any antiarrhythmic drug is to avoid adverse effects. Oral amiodarone can be used to achieve the absence of conversion, intravenous amiodarone provides a 50% rate of conversion of AF at 90 minutes with vernakalant.27 Faster conversion to sinus rhythm has been noted for the conversion of AF.36,37 A recent study compared oral flecainide (200–300 mg) or propafenone (450–600 mg) has been used as a “pill in the pocket” approach in patients initiating antiarrhythmic drugs other than dofetilide in the outpatient setting. High-dose oral flecainide (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%.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.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.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.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 Sotalol 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.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.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.50–52 Conversely, the benefit of these therapies in patients with congestive heart failure or multiple cardiovascular risk factors has been less robust.60 Similarly, the benefit of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for the secondary prevention of AF has not been demonstrated.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.59 Studies of statins for the primary or secondary prevention of AF have been conflicting and do not support specific antiarrhythmic recommendations.59,61 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.

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