Pharmacologic Management of Complex Arrhythmias in Patients with Implantable Defibrillators

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Introduction

Patients with implantable cardioverter-defibrillators (ICDs), placed for primary or secondary prevention of sudden cardiac death (SCD), often suffer from a variety of comorbid medical conditions. Although it has been well established that ICDs are the most effective method for prevention of SCD, these patients may develop a number of clinical arrhythmias for which the devices alone may be suboptimal. Frequent ICD shocks, whether appropriate or inappropriate, have been demonstrated to be associated with decreased quality of life, premature battery depletion, increased frequency of hospital admissions, and ultimately increased rates of death due to progressive heart failure (HF). In these circumstances, adjuvant pharmacologic therapy with antiarrhythmic drugs (AADs) is often warranted, and it has been estimated that AADs need to be initiated in 18% to 70% of patients with ICDs.

Patients with ICDs frequently develop supraventricular tachycardia (SVT). Many forms of SVT, such as atrioventricular (AV) nodal re-entrant tachycardia, atrial flutter, or atrial tachycardia, are amenable to radiofrequency catheter ablation. Others, such as atrial fibrillation (AF), may be more difficult to treat with ablation, especially in the presence of underlying structural heart disease. In patients who refuse ablation or when ablation is unsuccessful or not a viable option, AADs may be useful to maintain sinus rhythm.

Atrial fibrillation

AF is a common arrhythmia in patients with left ventricular dysfunction. The incidence of AF increases with severity of HF and has been reported to be as high as 50% in patients with New York Heart Association (NYHA) class IV symptoms. Patients with HF who have ICDs may be subject to inappropriate shocks due to a rapid ventricular response. Recurrent AF, with or without rapid ventricular response, in turn leads to...
Pharmacological rate control strategies include the use of β-blockers, calcium channel blockers, digoxin, or various combinations of these agents. Digoxin may be useful for rate control at rest, but is far less effective during activity. Rate control strategies may be ineffective or poorly tolerated in such patients. The absence of an “atrial kick” or the negative inotropic effects of calcium channel blockers and β-blockers may contribute to worsening HF. Therefore, it is often desirable to maintain sinus rhythm with AADs in this population. American College of Cardiology/American Heart Association/European Society of Cardiology guidelines assign intravenous amiodarone (see below) a class IIa recommendation for acute rate control in patients with AF when other measures are unsuccessful or contraindicated. Oral amiodarone is not appropriate first-line therapy for chronic rate control. If β-blockers, calcium channel blockers, or digoxin (alone or combined) are ineffective, AV junction ablation and pacemaker implantation may be preferable to chronic amiodarone therapy.12-13

When choosing AAD treatment for AF in patients with an ICD, a limited number of alternatives are available. Data from numerous studies, including the Cardiac Arrhythmia Suppression Trial (CAST) and the Cardiac Arrest Study Hamburg (CASH), among others, have demonstrated increased mortality with the use of class I AADs in patients with structural heart disease, especially those who are post myocardial infarction.14-16 Since the vast majority of ICD recipients fall into these categories, pharmacotherapeutic options in this population are quite restricted.

Amiodarone has been shown in numerous studies to be the most effective agent for maintenance of sinus rhythm in patients with AF.17-20 Amiodarone has been shown to maintain sinus rhythm at 12–16 months at a rate of 60–69%, versus 38–39% for sotalol.19,21 Although amiodarone is less effective for cardioversion, intravenous amiodarone has demonstrated effectiveness at conversion of AF to sinus rhythm within 6–8 h post initiation.22 In the Sotolol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) trial of 665 patients with persistent AF, oral amiodarone resulted in a 27% conversion rate to sinus rhythm at 28 days, compared with 24% for sotalol and 0.8% with placebo.17 The efficacy of amiodarone is offset by its numerous potential side effects, including thyroid toxicity, pulmonary fibrosis, hepatic and neurologic disturbances, often leading to discontinuation of the drug. For this reason, amiodarone is often reserved as a second-line agent for the management of AF.

Sotalol, a class III AAD with β-blocker properties, is better tolerated (fewer adverse effects) than amiodarone, and its effectiveness in treating atrial fibrillation has been evaluated in a number of clinical trials. In a randomized, double-blind study of 300 patients followed for 12 months, sotalol and propafenone were found to have significantly higher rates of sinus rhythm maintenance relative to placebo (73% and 63%, respectively, versus 35% for placebo).23 Another study looked at the safety and efficacy of various doses of d,l-sotalol (80, 120 and 160 mg twice daily) compared to placebo in 253 patients with atrial fibrillation and/or atrial flutter.24 Both the 120- and 160-mg dosage groups had significantly longer times to arrhythmia recurrence relative to placebo (229 days and 175 days, respectively, compared to 27 days for placebo). As noted above, in a head-to-head study, sotalol was shown to be less effective than amiodarone for maintenance of sinus rhythm.19,21 Because of sotalol’s non-selective beta blocking properties, it is a useful rate controlling agent in the event of AF recurrence,25 and is the preferred agent in patients with coronary artery disease.12 Owing to a significant risk of proarrhythmia (torsade de pointes, bradycardia, and heart block),26 it is generally recommended to hospitalize patients while initiating sotalol therapy, particularly in patients at risk of marked QT interval prolongation, and those with structural heart disease or renal insufficiency.

Dofetilide is a class III AAD that may be used in patients with left ventricular dysfunction. In the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) study, dofetilide resulted in conversion to sinus rhythm within 30 h of initiation in 87% of patients, and resulted in 58% maintenance of sinus rhythm 1 year after cardioversion.27 The Danish Investigations of Arrhythmias and Mortality on Dofetilide (DIAMOND) study of dofetilide use in patients with reduced left ventricular ejection fraction (LVEF) showed 79% maintenance of sinus rhythm at 1 year.28 Owing to QT prolongation with a resultant risk of torsade de pointes, dofetilide therapy must be initiated in a monitored hospital setting at doses titrated according to renal function and degree of QT interval prolongation.

Dronedarone is a new AAD approved by the US Food and Drug Administration (FDA) in July 2009. This agent acts on sodium, potassium, calcium channels, and has antiadrenergic properties, thereby expressing characteristics of all four Vaughan Williams classes of AADs.29 Dronedarone is a benzofuran analogue of amiodarone with structural modifications (such as removal of its iodine) implemented to avoid amiodarone’s plethora of potential toxicities.30 Dronedarone has been demonstrated to result in reduced hospitalization for AF.31 When directly compared to amiodarone, dronedarone was found to have higher rates of AF recurrence at 7 months (63.5 vs 42%), but was better tolerated with a lower rate of discontinuation.32 Dronedarone has been associated with increased rates of death from HF exacerbation in patients with NYHA class IV and NYHA class II or III HF (with a recent HF-related hospitalization) and is contraindicated in these patients.33 It has been associated with rare, but severe liver injury, including two cases of acute liver failure leading to liver transplant.34 A number of drugs are currently undergoing evaluation for use in AF. Vernakalant is an “atrial selective” mixed sodium and potassium channel blocker.35 Available in intravenous and oral forms, it has been shown to be effective in acute conversion of recent-onset AF (<7 days duration),36 and postoperative AF in patients following open heart surgery.37 However, to date no
head-to-head comparison with ibutilide (generally regarded as the “gold standard” for acute conversion) has been undertaken. Vernakalant has not been shown to be effective in the treatment of longstanding AF or for postoperative atrial flutter. Results of a recent study comparing intravenous vernakalant to amiodarone revealed vernakalant to be significantly faster than amiodarone in acute conversion of AF to sinus rhythm. Vernakalant converted 51.7% of patients to sinus rhythm within 90 min versus 5.2% of patients treated with amiodarone. Median time to conversion with vernakalant was 11 min. It has been shown to be safe, with minimal serious adverse effects. Its most common side effects have been transient dysgeusia, sneezing, nausea, and paresthesias. Intravenous vernakalant has been approved for use in Europe (trade name Brinavess) for rapid conversion of recent onset or postoperative AF, and is currently under FDA review in the United States. An unexpected case of cardiogenic shock forced investigators to halt enrollment for a late-stage IV vernakalant confirmatory study. The FDA stepped in and demanded to look over all the data before allowing the trial to recommence.

Azimilide, which (see above) has effects on both the rapid (I_kr) and slow (I_Ks) potassium channels, and has been found to be safe in patients with structural heart disease and a history of myocardial infarction. However, a number of trials have failed to demonstrate its efficacy at maintaining sinus rhythm in patients with either paroxysmal or permanent AF. It has also been associated with rare incidences of severe neutropenia (0.9%) and torsade de pointes (0.5%).

Ventricular tachycardia

Rates of VT in patients with ICDs vary depending on the indication for which the device was placed. Patients who have undergone ICD implantation for primary prevention have been found to have an annual rate of appropriate shocks of 5.1%, and a 35% rate of VT over 3 years. Secondary prevention ICD recipients have higher rates of subsequent VT, and are more likely to require recurrent ICD therapies if VT was their presenting arrhythmia, rather than VF. Among patients with ICDs for secondary prevention, those with a history of VT showed a 75.5% incidence of ICD therapy versus a 47.4% incidence for patients with prior VF over a 3-year period. Although there are relatively few controlled studies demonstrating their efficacy, the principal agents used in the treatment of VT to reduce ICD therapies are amiodarone and sotalol.

As noted above, sotalol is a β-blocker that exhibits class III antiarrhythmic activity at higher doses, and has been found to be effective in preventing ICD shocks in two prospective, randomized, placebo-controlled trials. In one study, sotalol reduced the risk of death or shock for any reason at 1 year by 48% compared to placebo. In addition, sotalol reduced the total number of shocks from 3.9 ± 10.6/year with placebo to 1.4 ± 3.5/year. A second study demonstrated a significant reduction in the incidence of sustained VT with sotalol therapy. Patients treated with sotalol had a 32.6% rate of VT/VF recurrence, versus 53.2% in the ICD only group (not treated with AADs). No difference in mortality was detected between these two groups.

The most commonly used, and most carefully studied, antiarrhythmic for the termination and prevention of VT is amiodarone. In the ARREST trial, 44% of patients with shock-refractory VF or pulseless VT treated with 300 mg IV amiodarone for out of hospital cardiac arrest survived to hospital admission, versus 34% with placebo. In a meta-analysis of all randomized trials on the efficacy of amiodarone in prevention of SCD in the pre-ICD era showed that it reduced mortality by 10–19%. This effect was similar for primary or secondary prevention. In a pooled database from two similar randomized clinical trials, amiodarone was evaluated for primary prevention in patients recovering from myocardial infarction. The incidence of cardiac death and arrhythmic death or resuscitated cardiac arrest was significantly lower in patients receiving amiodarone, if they were also being treated with concomitant β-blockers. There appeared to be no benefit to amiodarone over placebo in the absence of β-blockers. In contrast, the SCD-HeFT (Heart Failure Trial) trial showed no survival benefit to amiodarone for primary prevention in HF, despite a high use of β-blockers. The impact of amiodarone on total mortality in patients at risk of SCD is generally regarded to be neutral. As noted above, ICDs are the treatment of choice for primary and secondary prevention of SCD.

In patients who have already had an ICD implanted for inducible or spontaneous VT or VF and LVEF ≤40%, the Optimal Pharmacologic Therapy in Cardioverter Defibrillator Patients (OPTIC) study compared the efficacy at preventing shocks of amiodarone (200 mg) plus β-blocker with sotalol (240 mg) or β-blocker alone (bisoprolol 10 mg). During 1 year of follow-up, amiodarone plus β-blockers significantly reduced the risk of any shock compared to sotalol or β-blocker alone. Patients treated only with β-blockers had a 38.5% rate of shocks, while the rate was 24.3% with sotalol, and just 10.3% with amiodarone. We continue to recommend adjunctive amiodarone therapy to reduce frequent ICD discharges in patients already receiving beta-blockers.

Dofetilide, a class III AAD, has shown mixed results in the treatment of VT. In a pre-ICD era double-blind randomized crossover study in patients with ischemic heart disease and sustained VT, dofetilide was equally as effective as sotalol in preventing arrhythmia recurrence and arrhythmic death at 1 year. In a double-blind, placebo-controlled study in patients with ICDs, it prolonged the median time to first ICD intervention (antitachycardia pacing or shock) for VT or VF. However, dofetilide use was also associated with an increased incidence of torsade de pointes in this study. Use of dofetilide for VT/VF has been largely abandoned.

Azimilide, which (see above) has effects on both the rapid (I_kr) and slow (I_Ks) potassium channels, has shown promising results in the prevention of VT and VF. In one randomized, placebo-controlled trial of 172 patients with ICDs, azimilide reduced appropriate ICD therapies by...
of July 2011. In a larger study involving 633 patients with ICDs, the Shock Inhibition Evaluation with Azimilide (SHIELD) trial, azimilide showed a 57% risk reduction of recurrent VT or VF at a dose of 125 mg and a 47% reduction at 75 mg, compared with placebo during 1 year of follow-up. Other AADs for the prevention of VT have been studied to a very limited degree, if at all. In a small study of 76 patients with LVEF ≤40% due to ischemic or non-ischemic causes, dronedarone at various doses (600, 800, and 1,000 mg twice daily) was compared with placebo. Patients treated with dronedarone had a 39% incidence of appropriate ICD therapy, compared with 67% of those in the placebo group. However, results from the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) trial, which showed increased mortality with dronedarone in patients with advanced HF, would likely prevent its use for VT in most ICD patients. Celivarone is a new drug with electrophysiological effects similar to dronedarone. There is one ongoing randomized trial comparing this drug with amiodarone and placebo for the prevention of ICD interventions and death, with a projected completion date of July 2011.

**Potential drug-device interactions**

Antiarrhythmic drugs can have a variety of effects on the functionality of ICDs, and it is important to be aware of their effects prior to initiation (Table 1). These effects could result from the AADs' effects on the clinical tachyarrhythmias, or could be the direct result of capture or defibrillation threshold alterations by the AAD. Some effects are beneficial, while others may be detrimental, and close monitoring is advised after starting a new AAD.

The most important interaction to be aware of is the potential for AADs to alter the ICD’s defibrillation threshold (DFT). The DFT is the minimum amount of energy required to reliably convert VF to a supraventricular rhythm. The majority of AADs, including sotalol, dofetilide and azimilide, have been demonstrated to lower DFTs to a mild degree. This effect may be beneficial in patients whose DFTs are elevated or marginal at baseline. A small reduction after initiation of an AAD may provide an adequate safety margin (generally accepted to be 10 or more joules less than the device’s maximum output). In contrast, amiodarone has repeatedly been shown to result in a modest increase in DFTs. Interestingly, it has been demonstrated in an animal model that desethylamiodarone, an active metabolite of amiodarone, causes a greater increase in DFTs than the parent drug. The accumulation of this active metabolite during long-term therapy may explain the difference in DFTs with acute and chronic amiodarone therapy. Therefore, it may be advisable to retest DFTs in patients once they have achieved steady-state levels of amiodarone.

Rather than complete suppression of VT, AADs may result in lengthening of the VT cycle length. This can have beneficial and detrimental effects. Slowing of the VT rate may make it better tolerated hemodynamically, leading to fewer symptoms of dizziness and fewer syncopal episodes. Additionally, it can allow for more effective antitachycardia pacing, obviating the need for shocks to terminate VT. Conversely, the VT rate may be slowed so much that it is below the lower rate cut off for ICD detection, and therapy may not be delivered. Adjusting the tachyarrhythmia detection interval below the new tachycardia rate may solve this problem. However, lowering it too far may lead to inappropriate therapy if sinus tachycardia and VT rates overlap. This effect is most prominent with amiodarone, which may prolong VT cycle length by as much as 20%.

Antiarrhythmic drugs may have other effects on device parameters that could lead to poor function or early battery depletion. A number of AADs, especially class I agents and amiodarone, have been found to increase pacing thresholds. Additionally, thresholds increase with faster pacing rates, and may be significantly higher during ATP than at baseline. This should be considered when programming ATP output, and it is advisable to program the maximum output during ATP to ensure an adequate capture safety margin. Finally, AADs may lead to a slowing of the intrinsic sinus rate, resulting in frequent pacing. This could also lead to premature battery depletion, pacemaker syndrome (in single-chamber devices), or further impairment of LV dysfunction. In such cases, parameter adjustments, such as lowering the pacing rate or prolonging the AV delay, should be implemented to minimize these effects as much as possible.

**Conclusions**

Although ICD therapy is the treatment of choice for primary and secondary prevention of SCD in patients with a cardiomyopathy, these patients often go on to

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**Table 1: Potential drug-device interactions.**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Change/Raise/DFT</th>
<th>Prevents</th>
<th>Prevents</th>
<th>Increases</th>
<th>Decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowing of ventricular tachycardia cycle length</td>
<td>DFT</td>
<td>Increase</td>
<td>ATP output</td>
<td>Pre-shock</td>
<td>Post-shock</td>
</tr>
<tr>
<td>Increase in ventricular pacing threshold</td>
<td>DFT</td>
<td>Increase</td>
<td>ATP output</td>
<td>Pre-shock</td>
<td>Post-shock</td>
</tr>
<tr>
<td>Induced bradycardia due to changes in sinus rate or atrioventricular conduction</td>
<td>DFT</td>
<td>Increase</td>
<td>ATP output</td>
<td>Pre-shock</td>
<td>Post-shock</td>
</tr>
</tbody>
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develop a wide range of complex arrhythmias. Many of these may be amenable to radiofrequency catheter ablation, but for those that are not, adjuvant AADs may be required. The main goal of treatment with AADs is prevention of ICD shocks, which have an adverse effect on quality of life, lead to an increase in hospital admissions, and are ultimately associated with progression of HF leading to death. A wide range of AADs are available, but the most effective in this category of patients are class III drugs, particularly amiodarone. A number of new drugs are currently being investigated, which may provide further effective options with a reduction in potential adverse effects. While pharmacologic treatment may be successful in controlling the target arrhythmias, the treating physician must anticipate the potential for these drugs to interfere with the patient’s device function. This will often require close monitoring, repeat testing, or an alteration of the pharmacologic regimen.

References


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