Filling the Need for New Antiarrhythmic Drugs to Prevent Shocks From Implantable Cardioverter Defibrillators*

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The implantable cardioverter defibrillator (ICD) has had an enormous impact on the treatment of patients with life-threatening ventricular arrhythmias. It has been shown not only to be effective in reducing mortality in patients who have survived a potentially life-threatening ventricular arrhythmia (1) but also to improve outcomes when used as primary prevention for sudden cardiac death in patients with ischemic cardiomyopathies (2–4). However, an ongoing problem with ICD therapy is recurrent shocks that occur in some patients. Inappropriate shocks can occur because of problems with the defibrillator lead itself or from supraventricular tachyarrhythmias, most commonly atrial fibrillation (AF). In addition, patients can receive recurrent appropriate shocks for the ventricular arrhythmias for which the ICD was originally implanted. Although such shocks can be life saving, they can be painful and emotionally traumatic for the patient, particularly if they are frequent.

Antitachycardia pacing is often effective in terminating ventricular tachycardia (VT), even when programmed empirically (5). Particularly for slower, more stable episodes of VT, antitachycardia pacing can terminate all or most episodes of VT, often with the patient unaware that the arrhythmia even occurred. Recently, antitachycardia pacing has also been shown to be effective for more rapid, hemodynamically unstable episodes of VT (6). However, there are patients who experience frequent shocks for polymorphic VT or ventricular fibrillation (VF) for which antitachycardia pacing is ineffective. In addition, antitachycardia pacing may be ineffective for the termination of VT or only partially effective so that patients may continue to experience recurrent ICD shocks even though the majority of arrhythmia episodes may be terminated with pacing.

Another option for control of frequent shocks from ICDs is radiofrequency catheter ablation. Although catheter ablation of VT is effective in many patients (7), the procedure is long and technically demanding. There are often multiple tachycardias present, which can make mapping and ablation of individual tachycardias difficult. Hemodynamically unstable arrhythmias create challenges as well, in that patients cannot tolerate the arrhythmias for any length of time, often making point-by-point mapping impossible. Although techniques to ablate the substrate for VT by mapping regions of unexcitable scar and creating ablation lines across potential areas where reentrant circuits can develop are promising, these procedures can still realistically be performed only in relatively small numbers of experienced centers. For all these reasons, adjunctive antiarrhythmic drug therapy is necessary in many patients with implanted defibrillators for control of recurrent ventricular tachyarrhythmias.

It has been estimated that 20% to 50% of patients with ICDs require adjuvant antiarrhythmic drug therapy (8). In the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, 18% of patients in the ICD arm received antiarrhythmic drugs in follow-up (9). Because antiarrhythmic drug treatment in the trial was considered a crossover, this percentage should be considered an absolute minimum of the number of patients with ICDs who are likely to require antiarrhythmic drugs. The AVID trial included only patients with a history of life-threatening ventricular arrhythmias. With the increasing use of ICDs for primary prevention of sudden cardiac death, it might be presumed that the frequency of shocks in follow-up will be lower. However, supraventricular tachyarrhythmias are frequent in patients with serious structural heart disease for whom prophylactic ICDs are considered, making it likely that a significant proportion of patients will still require adjuvant drug therapy for arrhythmias.

Amiodarone is the most commonly used drug for the prevention of shocks in implanted defibrillators. One of the more important reasons for its frequent use when drug therapy is necessary is the fact that amiodarone is safe to use in patients with poor ventricular function (10). Although it is widely considered to be an effective drug for prophylaxis against frequent shocks, there are surprisingly few studies that demonstrate this. In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (CASCADE) study (11), patients with ICDs who received amiodarone experienced fewer appropriate shocks from their defibrillators than patients treated with conventional antiarrhythmic drugs. However, it cannot be determined from this study whether the amiodarone actually reduced the number of shocks or the conventional antiarrhythmic drugs were proarrhythmic.

Although amiodarone is currently the most commonly prescribed drug for treatment of frequent shocks in patients with ICDs, patients often develop serious side effects such as pulmonary fibrosis, necessitating discontinuation of the drug. There are then few other options for treatment, particularly in patients with symptomatic heart failure.

Class I antiarrhythmic drugs may be proarrhythmic and are not as effective as amiodarone (11). A recent study...
investigated the use of dofetilide, a newer class III antiarrhythmic drug, for the prevention of shocks from implanted defibrillators. In a double-blind, placebo-controlled study in patients with ICDs, dofetilide did not affect the time to first ICD intervention (antitachycardia pacing or shock) for VT or VF (12). This finding is unfortunate, inasmuch as dofetilide is the only drug aside from amiodarone that has been demonstrated not to affect survival adversely in patients with serious structural heart disease (13).

Sotalol, however, which is another class III antiarrhythmic drug, has been found effective in preventing shocks from ICDs. In a prospective, randomized study, patients who received ICDs for documented ventricular arrhythmias were given sotalol or placebo and followed up for 12 months (14). Sotalol reduced the risk of a first shock for any reason or death by 48% compared with placebo (p < 0.001). At one year, 66% of patients receiving sotalol versus 46% of patients receiving placebo were free of the primary end point. The frequency of shocks was reduced from 3.9 ± 10.6/year with placebo to 1.4 ± 3.5/year with sotalol. The drug was effective in reducing the frequency of both appropriate and inappropriate shocks. Sotalol has thus been shown to be an effective drug for prophylaxis against recurrent arrhythmias in patients with ICDs. However, in the study described earlier, 66% of the patients had ejection fractions >30%. Many of the patients who are most in need of antiarrhythmic drugs to prevent shocks from ICDs have poor ventricular function and cannot tolerate the negative inotropic effects of sotalol. If these patients have intolerable side effects from amiodarone or the drug has been ineffective, there are really no other good options for treatment. Atioventricular nodal blocking drugs can be used to prevent detection and treatment of supraventricular tacharyrhythmias, but other drugs for the prevention of ventricular arrhythmias are sorely needed.

Azimilide is a class III antiarrhythmic drug under investigation for the treatment of supraventricular and ventricular arrhythmias. It blocks both the rapid (IKr) and the slow (IKs) components of the delayed rectifier cardiac potassium channel. It has been demonstrated to be effective in the treatment of AF (15). In this issue of the Journal, a pilot study of the efficacy of azimilide in reducing the frequency of ventricular arrhythmias in patients with ICDs is reported (16). Patients eligible for the study either had both an implanted defibrillator and at least one shock over the preceding year or had documented VT or VF and inducible VT or VF with noninvasive programmed stimulation through the ICD. There were 172 patients who were randomized to treatment with either placebo or one of three doses of azimilide (35, 75, or 125 mg/day) and followed up for 12 months. The patients enrolled in the study had a high frequency of ICD therapies. There were 2,011 appropriate therapies, with a mean of 18 ± 50 per patient and a median of 4. There were 358 appropriate shocks, with a mean of 4 ± 5 per patient and a median of 2. The mean ejection fraction was approximately 31%, with 62% of the patients having an ejection fraction <35%.

The frequency of appropriate shocks and antitachycardia pacing was significantly decreased in patients who received an active drug, with efficacy seen at all three dose levels. Azimilide reduced the frequency of appropriate ICD therapies by 69% compared with placebo (hazard ratio 0.31, p = 0.0001). Importantly, azimilide was well tolerated and did not affect the ejection fraction or defibrillation threshold. The fact that ICD therapies were reduced at all three dose levels is interesting in light of the fact that azimilide has been shown to be effective for the prevention of AF only at doses of 100 or 125 mg/day (15). If the efficacy of azimilide at relatively low doses can be confirmed in a larger study, it would clearly be an advantage in minimizing the risk of side effects.

There were few adverse events reported. Only two patients had torsades de pointes, an important observation with a drug that can prolong the QT interval. Possible proarrhythmia, defined as new VT or an increased frequency of VT, was equally common in the placebo group when compared with all three dose groups.

Although this study was a pilot study, the observation that azimilide significantly reduced the frequency of ICD therapies in a patient population with a high incidence of recurrent ventricular arrhythmias is an important one. New antiarrhythmic drugs for reducing the frequency of ICD therapies are crucially needed for many reasons. Shocks from ICDs are uncomfortable for patients and have a negative impact on quality of life. In addition, frequent episodes of VT or VF can adversely affect cardiac function, whereas frequent shocks can affect battery longevity in ICDs. The results of this pilot study are intriguing but need to be confirmed in a larger patient cohort. Such a study, the Shock Inhibition with Azimilide (SHIELD) study, is currently in progress to confirm the results of the pilot study. If the favorable effect of azimilide on arrhythmic events in patients with ICDs can be confirmed, the availability of a new drug to manage these vexing clinical problems will be most welcome.

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