The Shocking Story of Azimilide

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Initially tested for the secondary prevention of life-threatening ventricular arrhythmias in survivors of cardiac arrest,1 the effectiveness of implantable cardioverter-defibrillator (ICD) therapy has recently been validated for the primary prevention of sudden cardiac death in high-risk patients with left ventricular (LV) dysfunction.2,3 Despite an improvement in survival (30% relative risk reduction) comparable to that of β-blockers4 or angiotensin-converting enzyme (ACE) inhibitors,5 ICD therapy remains limited by impairment in quality of life in some of its recipients. As may be expected, the psychosocial consequences of device implantation, including anxiety disorders, depression, phobias, and sexual and employment problems, have been linked to the frequency of ICD discharges.6 In a recent publication, Godemann et al7 demonstrated a 3-fold increase in panic disorders and agoraphobia in patients with ≥2 ICD shocks annually. When severe enough, these symptoms necessitate psychiatric intervention8 or, in extreme cases, even device explantation.

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Enhancements in detection algorithms have reduced the rate of inappropriate shocks for supraventricular arrhythmias,9 and the empirical programming of antitachycardia pacing (ATP) has proved effective in reducing the frequency of shocks for conversion of ventricular tachycardia (VT). Nevertheless, ATP has been routinely programmed only in patients with slower VTs, despite recent data suggesting its effectiveness as an initial therapy in faster VTs up to 250 bpm. In the PainFREE Rx (Does PaciNg Fast VT REDucE Shock Rx) trial, this strategy of “aggressive” programming resulted in a significant improvement in quality of life without compromising patient safety,10 further confirming the negative impact of recurrent shocks on psychosocial functioning. Regardless of programming preferences, ATP therapy is ineffective in some patients, particularly those with polymorphic VT or ventricular fibrillation (VF).

Radiofrequency catheter ablation of recurrent symptomatic monomorphic VT is an alternative form of palliation in patients with frequent ICD discharges. Despite good success rates in selected patient populations and the development of new techniques for the ablation of hemodynamically unstable VTs,11 these strategies remain limited mostly to patients with stable inducible VT evaluated in experienced centers.

The limited effectiveness of nonpharmacological therapies in reducing ICD shock frequency has prompted the use of antiarrhythmic medications in ICD recipients with a significant burden of symptomatic ventricular arrhythmias. In addition to reducing appropriate shocks, antiarrhythmic drug therapy may decrease the likelihood of inappropriate ICD discharges that are triggered by supraventricular arrhythmias. Type III antiarrhythmic drugs also may reduce the defibrillation threshold. Unfortunately, the same clinical characteristics that predispose ICD recipients to sudden cardiac death and recurrent shocks limit the choice of antiarrhythmic drugs because of important safety considerations. In a study by Whang et al,12 the combination of NYHA class III heart failure symptoms and LV ejection fraction <20% resulted in a particularly elevated risk of appropriate shocks in patients with primary and secondary preventive indications for ICD implantation. These results, along with findings from subanalyses of the 3 large secondary prevention ICD trials, suggest that adjunctive antiarrhythmic therapy is needed most in patients with advanced structural heart disease.13

In this patient population, Vaughn Williams class IA and IC agents are problematic because of their reduced efficacy and proarrhythmic propensity,14 leaving β-blockers and class III agents as preferred therapies. Class III antiarrhythmic drugs are a heterogeneous group of agents that affect repolarization, thereby prolonging action potential duration and refractory periods. Whereas sotalol and dofetilide produce these effects through blocking the rapidly activating outward K+ current Ikr, amiodarone and azimilide block both Ikr and the slowly activating component of the delayed rectifier K+ current Iks. Differences in selectivity toward the various cardiac K+ channels and reverse use–dependence characteristics (greater blocking effect at slower heart rates) of the drugs may influence their proarrhythmic profile.15

In a study by Pacifico et al,16 sotalol was shown to be effective in reducing the risk of death or the delivery of a first defibrillator shock in patients with documented life-threatening ventricular arrhythmias. In addition, when compared with placebo, sotalol resulted in a significant 63% decrease in the mean frequency of all-cause shocks during a 12-month period. Interestingly, sotalol was discontinued in almost one third of the patients, mostly because of adverse events. Given that the study predominantly included patients with mild to moderate LV dysfunction, it is conceivable that the adverse hemodynamic and electrophysiological effects of sotalol would be more pronounced in a population with advanced structural heart disease, further limiting its use for the prevention of frequent ICD shocks in such patients. In a more recent study, Kettering et al17 showed metoprolol to be as efficacious as sotalol for the prevention of recurrent VT in
ICD recipients. These findings, along with previously published data demonstrating a significant reduction in mortality with β-blockers in patients with heart failure, suggest that initiating or increasing β-blockade is preferable to sotalol as an initial therapy of recurrent ICD shocks.

Another antiarrhythmic drug commonly used in this setting is amiodarone. Despite the lack of randomized studies demonstrating its efficacy for recurrent defibrillator shocks, amiodarone is widely used because of its favorable safety and tolerability profiles. Unlike sotalol, however, amiodarone can raise defibrillation thresholds and lead to serious long-term adverse effects, most notably pulmonary fibrosis.

Azimilide is an investigational class III agent with electrophysiological effects on the repolarization phase of the cardiac action potential that are similar to amiodarone. As such, it is anticipated that the proarrhythmic potential of azimilide would be low. Studies of azimilide for the treatment of atrial fibrillation show an overall incidence of torsade de pointes of only 0.5% and are consistent with this expectation. In addition, azimilide decreases the defibrillation threshold and does not have β-blocker side effects, which are potential advantages over amiodarone and sotalol, respectively. Therefore, azimilide would seem attractive for the prevention of ICD shocks in patients with recurrent VT.

In this issue of Circulation, Dorian et al report on the efficacy and safety of azimilide in reducing symptomatic tachyarrhythmias recurrences and ICD therapies in patients with ICDs. Patients were eligible for participation in the study if they had documented spontaneous VT or VF in the setting of an ejection fraction that was ≤40% before ICD implantation or if they had a preexisting ICD and a subsequent shock in the 6 months preceding enrollment. Patients with baseline long QTc and those with severe advanced heart failure (NYHA class IV) were excluded. Antiarrhythmia pacing was programmed in the lowest VT detection zone, whereas only shock therapies were delivered above 200 bpm.

A total of 633 patients were randomly assigned to placebo or 1 of 2 doses of azimilide (75 or 125 mg/d) and observed for 12 months. The 2 coprimary end points of the study were all-cause shocks and a composite end point of all-cause shocks plus symptomatic tachyarrhythmias terminated by ATP. Symptomatic arrhythmias were documented before ICD interrogation on the basis of patient-reported symptoms of dizziness, dyspnea, palpitations, presyncope, or syncope.

Most (91%) patients included were in NYHA classes I or II, with a mean LV ejection fraction of 35%. β-Blockers, ACE inhibitors, and statin therapies were used in 60% to 80% of patients. The total number of ICD events was 4 shocks per patient-year in the placebo group. Treatment with azimilide 75 and 125 mg/d resulted in significant 57% and 47% decreases in all-cause shocks plus symptomatic tachyarrhythmias terminated by ATP compared with placebo. The difference in this end point between the 2 doses of azimilide did not reach statistical significance. Importantly, neither dose of azimilide reduced the number of all-cause shocks. Moreover, the proportion of patients who were free of ICD shocks at the conclusion of the study did not differ significantly among the 3 groups. Azimilide was well tolerated, with discontinuation rates that were comparable in the treatment and placebo groups. The incidence of torsade de pointes in patients receiving azimilide was relatively low (5 patients, 1%), although slightly higher than that observed in previous studies.

The data from this well-conducted clinical trial are derived from statistical models that account for the nonuniform temporal distribution of events. Their methods should serve as a model for future studies of this type. The data clearly support the authors’ conclusion that azimilide reduces symptomatic episodes of VT/VF in patients with ICDs; however, they leave other questions unanswered. The primary goal of antiarrhythmic therapy in patients with ICDs is palliation. VT terminated by ATP usually produces mild symptoms that may not have much of an adverse affect on quality of life. Thus, the composite end point used in the study by Dorian and associates may not be the most clinically useful one. The inability of the drug to reduce shocks adds to this uncertainty because shocks have been clearly associated with worse outcomes in patients with ICDs. Azimilide reduced the number of cardiac-related emergency department visits and hospitalizations, which suggests that it did indeed improve patients’ status. This observation is difficult to interpret, however, because the benefit was significant only for the lower azimilide dose. It is unfortunate that additional psychosocial data were not gathered in the trial. It also would have been helpful to determine whether azimilide reduced the frequency of “electrical storm” events (multiple shocks during a brief period) because these are often a cause of psychological distress.

More than 75% of all patients in this trial experienced adverse events, and these events caused the study drug to be discontinued in >35% of the subjects. These observations underscore some of the challenges of studying and providing care for this very ill patient population.

Many patients with ICDs need suppressive antiarrhythmic therapy, and the currently available options are not adequate. The study by Dorian and colleagues shows that azimilide is a safe, well-tolerated, and effective treatment for VT/VF in patients with ICDs. Even without definitive data on patient outcomes, this agent may well prove to be a useful addition to the pharmacopoeia.

References


Key Words: Editorials • defibrillation • tachyarrhythmias • pharmacology • antiarrhythmia agents
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Circulation. 2004;110:3624-3626
doi: 10.1161/01.CIR.0000151357.36405.72
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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