

REVIEW

Advantages and Pitfalls of Combining Device-Based and Pharmacologic Therapies for the Treatment of Ventricular Arrhythmias: Observations from a Tertiary Referral Center

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Introduction

Implantable cardioverter defibrillators (ICDs) have proven to be highly successful for treating life-threatening ventricular arrhythmias. Rapid improvements in the design and technology of ICDs and defibrillator leads have improved efficacy and accuracy of delivered therapy. The ICD has become the treatment of choice for patients at risk of life-threatening ventricular arrhythmias. This has largely relegated antiarrhythmic drug therapy to a palliative role in the treatment of ventricular arrhythmias, that is, preventing inappropriate or frequent shock therapy. However, despite the proven efficacy of ICD therapy for treating ventricular arrhythmias, pharmacologic therapy still remains an important adjunctive treatment to device-based therapy. The use of antiarrhythmic drug therapy, in combination with an ICD, has unique implications whereby beneficial and adverse interactions may occur. Therefore, it is important for the physician managing these patients to be fully aware of these potential interactions. This article summarizes the benefits and adverse effects of combining device-based antiarrhythmic therapy with antiarrhythmic drug therapy. In addition, a framework is provided, drawn from the authors' experience, on which to tailor the safe management of concurrent antiarrhythmic drug therapy and device-based therapy.

Trends of Antiarrhythmic Drug Use in Patients Implanted with an ICD

To better assess prior and current use of antiarrhythmic drug therapy in patients with an ICD, results were reviewed of snapshot surveys performed at the authors' tertiary care center in 1989, 1993, 1997, and 2000. At each point in the survey,

the study identified if a patient implanted with an ICD was also receiving an antiarrhythmic drug and the reason for institution of the drug therapy. The surveys documented a dramatic decrease in antiarrhythmic drug therapy use in the beginning of the past decade. Currently, about 40% of the patients followed at the University of Pennsylvania Health System with an ICD are also receiving an antiarrhythmic drug (Fig. 1).¹ It is interesting to speculate about the reasons why antiarrhythmic drug therapy use was dramatically reduced in this patient population at the beginning of the 1990s. An analysis of the relationship between arrhythmia presentation and antiarrhythmic drug therapy use in the patients with an ICD demonstrated a decrease in antiarrhythmic drug therapy use in patients with cardiac arrest/syncope. However, the use of antiarrhythmic drug therapy for patients with sustained ventricular tachycardia (VT) remained relatively constant over the last decade. Specifically, antiarrhythmic drug use decreased from 71% to 33% between the years 1989 and 2000 in patients presenting with cardiac arrest or syncope to the authors' center. In contrast, its use was relatively unchanged in patients presenting with uniform sustained VT (46% in 1989 vs 54% in 2000) (Fig. 2).¹ The authors believe these observations primarily reflect a change in their approach to patients who present with cardiac arrest. The decreased use of antiarrhythmic drug therapy in patients with cardiac arrest/syncope probably reflects their increasing use of ICDs as a first line therapy in this patient population. This is probably due to the fact that pharmacologic therapy in these patients is no longer guided by the response to invasive programmed stimulation, but rather it is based on the frequency of arrhythmia recurrences or the need to suppress supraventricular arrhythmias. Other factors that may have also contributed to the reduced use of antiarrhythmic drug therapy in patients implanted with an ICD include technological improvements in the devices themselves, particularly the introduction of antitachycardia pacing. Improvements in

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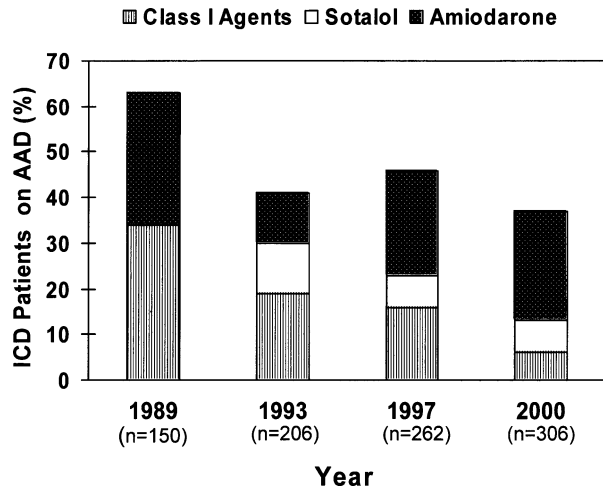


Figure 1. Trends of antiarrhythmic drug use over the past decade in patients with an ICD. Overall, there was a decrease in the use of antiarrhythmic drugs, which occurred at the beginning of the last decade and then leveled off. The largest decrease of drug therapy in this patient population was seen with the Vaughn-Williams Class I agents. However, there has been an overall increase in the use of the class III agents amiodarone and sotalol. Data were sampled at regular 4-year intervals between the years 1989 and 1997. However, due to the rapid advancements in ICD technology and expanded indications for ICD implantation in the late 1990s, the last follow-up was performed at a slightly earlier time interval. ICD = implantable cardioverter defibrillator; n = number of patients with an ICD.

nonpharmacologic management of associated supra-VTs at the beginning of the last decade, specifically radiofrequency catheter ablation, also contributed to the decreased use of antiarrhythmic drug therapy in these patients.

The use of antiarrhythmic drug therapy appears to vary significantly from one institution to another. Various studies have reported the use of antiarrhythmic drug therapy in patients implanted with a prior ICD, where the percentage of ICD patients receiving pharmacologic therapy ranges from 18% to 70%.^{2,3} Although it is worthwhile reflecting on representative institutional antiarrhythmic drug usage, it is probably more useful to take a minimalist point of view with identification of the smallest percentage of patients with an antiarrhythmic device that will require pharmacologic therapy. Data on this parameter, the authors believe, was most accurately reflected by the Antiarrhythmic versus Implantable Defibrillators (AVID) trial. Since crossover was discouraged in this trial, the number of patients randomized to the ICD arm who required drug therapy should be a close approximation of the absolute requirement for antiarrhythmic drug therapy in this pa-

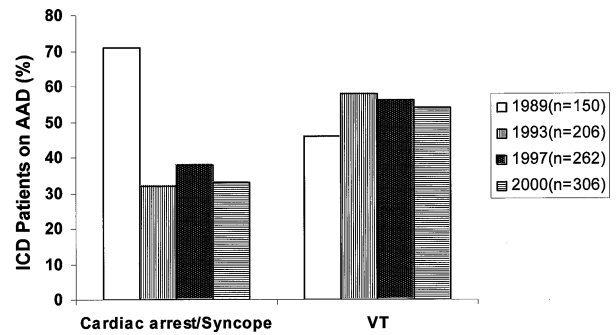


Figure 2. Influence of ventricular arrhythmia diagnosis on the use of antiarrhythmic drugs over the past decade at the University of Pennsylvania Health System. The decrease in antiarrhythmic drug use has occurred primarily in patients with a diagnosis of cardiac arrest or syncope and has remained relatively constant in those patients with a diagnosis of unimorphic ventricular tachycardia.

tient population. The ICD arm of the AVID study showed that 81 (18%) of the patients, out of a total of 461 patients with an ICD, subsequently required treatment with an antiarrhythmic drug during a median follow-up of 135 days. The primary reasons for crossover in this trial were frequent ICD shocks in 64%, recurrent ventricular arrhythmia in 26%, and recurrent SVT in 2% of these patients.⁴ In another recent randomized ICD trial, Multi-center Automatic Defibrillator Implantation Trial (MADIT) II, 16% of the patients in the defibrillator arm were on an antiarrhythmic drug at the time of the last follow-up visit.⁵ These data confirm the important role that hybrid therapy, use of an antiarrhythmic device combined with pharmacologic therapy; contribute to the management of life-threatening ventricular arrhythmias. Even with all the present day advances in ICD technology, it is reasonable to assume that at least 16–40% of patients implanted with an ICD will require additional pharmacologic therapy based on the trials referenced above. In addition, there is lack of data in the literature on compliance of antiarrhythmic drug usage in patients with an ICD. For this reason, it is critical that the managing physician be aware of all of the important interactions between an antiarrhythmic device and antiarrhythmic agent in this patient population.

Beneficial Effects of Combining Antiarrhythmic Drug Therapy with ICD Therapy
Suppression of Recurrent Arrhythmias

Antiarrhythmic drug therapy is primarily initiated to prevent recurrence of ventricular malignant arrhythmias in patients implanted with an ICD, but may be useful for several additional

Table I.
Potential Beneficial Effects of Combining Antiarrhythmic Drugs with ICD Therapy

- Suppression of recurrent episodes of VT/VF with a reduction in the number of delivered shocks and prolongation of the device's battery life.
- Prolongation of the tachycardia cycle length resulting in increased hemodynamic tolerance and successful termination by antitachycardia pacing.
- Prevention or decrease in the frequency of paroxysms of supraventricular tachycardia resulting in a reduced number of inappropriate ICD shocks.
- Decrease the frequency of symptomatic nonsustained VT episodes.
- Prevention and/or improved treatment of electrical storm.

ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

reasons in these patients (Table I).^{6,7} The frequent recurrence of arrhythmias can result in multiple ICD shocks that produce patient discomfort and premature device battery depletion. Antiarrhythmic drugs also prevent frequent paroxysms of supra-VT that may lead to inappropriate delivery of device therapy.⁸ Furthermore, most antiarrhythmic drugs tend to increase the tachycardia cycle length, which may render the tachycardia more amenable to antitachycardia pacing therapy and spare the patient from uncomfortable shock therapies. This is exemplified in a study by Mazur et al.⁹ that showed that in patients with documented monomorphic VT there was a better response to overdrive pacing in the presence of dofetilide (Vaughan Williams Class III agent) as compared to patients treated with ICD-based therapy alone.

The importance of suppressing arrhythmia events in patients with a preexisting ICD should not be underestimated. In the European Registry of Implantable Defibrillator (EURID) study, investigators collected and analyzed data from 3,344 patients implanted with an ICD to assess the mortality, morbidity, and complications associated with these devices. Data sets were collected at the time of device implantation, the time of hospital discharge, and then at 3-month and 12-month intervals following hospital discharge. Overall, almost one half of these patients had some form of device-based intervention during the course of the study. In addition, 1,691 hospital readmissions were recorded during the 12-month follow-up interval with 61.3% of the readmissions due to appropriately treated recurrent ventricular arrhythmias.¹⁰ The antiarrhythmic agents most commonly used in this registry were amiodarone (16.8%) and sotalol (6.5%) at the time of device implantation that subsequently increased to 19.8% and 10.4% of the patients, respectively, at the conclusion of the follow-up. The results of this study suggest that hospital readmission due to appropriate ICD therapy still remains a significant clinical issue.

Preventing Psychological Effects of ICD Shock therapy

Delivery of an ICD shock, appropriate and inappropriate, is often associated with increased psychological distress in the patient and their families.^{11–13} The AVID trial extended these findings by demonstrating that patients who received more than one ICD shock within the initial year of implantation reported significant declines in physical functioning and mental well being.¹⁴ Increased sadness, anxiety, fatigue, and nervousness were also found to be associated with more ICD discharges.¹⁵ One study reported that overall psychological distress was significantly correlated with the total number of ICD shocks a patient receives.¹⁶ Taken together, these studies suggest that a reduction in ICD shock frequency may prevent psychological stress and lead to an improved quality-of-life for ICD recipients.

Helping to Manage Ventricular Electrical Storm

The precise definition of electrical storm is still evolving. Credner et al.¹⁷ and Exner et al.¹⁸ defined electrical storm as the occurrence of three or more separate episodes of VT/ventricular fibrillation (VF) within a 24-hour period where each episode is separated by at least 5 minutes. The most commonly used definition of electrical storm is two or more episodes of hemodynamically destabilizing VT/VF occurring in a 24-hour period that usually require electrical cardioversion or defibrillation.^{19,20} Most published data suggest that approximately 10–30% of patients with an ICD experience electrical storm at some point in their clinical course.^{17,21} The etiology of electrical storm is not clearly understood, but acute ischemia, worsening cardiac function, the development of electrolyte disturbances, autonomic imbalance, and drug induced proarrhythmia are all considered to be precipitating factors. The majority of patients who experience electrical storm require in-hospital therapy, thus significantly impacting ICD related treatment costs.¹⁷ In one study,

electrical storm appeared to identify ICD recipients who were at higher risk for a nonsudden mechanism of death, particularly within the first 3 months after occurrence of the event.¹⁸ In addition, another study reported that the occurrence of appropriate, multiple high energy discharges were common during electrical storm and were associated with a poorer clinical outcome.²¹

In patients presenting with electrical storm, attention should be paid to correcting potentially reversible triggering factors before specific antiarrhythmic drug therapy is instituted. Myocardial ischemia and increased sympathetic output are common precipitating factors in this situation, and the authors feel that initiating or intensifying therapy with β -adrenergic blockers should be attempted whenever possible. If further antiarrhythmic drug therapy is necessary, intravenous amiodarone can be administered followed by oral maintenance doses. This strategy has been reported to produce successful short-term results with long-term outcomes similar to patients without electrical storm who have a similar degree of left ventricular dysfunction.¹⁷ The efficacy of amiodarone in the treatment of unstable VT/VF is fairly well established by several clinical trials,^{19,20} but its effect in patients with an existing ICD in preventing electrical storm has not been evaluated in a randomized study.

In one case report, the class I antiarrhythmic agent mexiletine was reported to have successfully terminated electrical storm in combination with amiodarone.²² In another case report, biventricular pacing was found to be useful in preventing recurrent episodes of VT that were refractory to antiarrhythmic drug.²³ While, antiarrhythmic drug therapy used in combination with an ICD may be useful for treating electrical storm it is clear that the available data is scant. In addition, even less evidence exists about the usefulness of antiarrhythmic drug therapy in conjunction with a biventricular ICD, which is increasingly replacing the standard right-sided single chamber and dual chamber devices.

Decrease in Defibrillation Threshold

In most situations antiarrhythmic drug therapy increases the energy requirement for defibrillation. However, some antiarrhythmic drugs may actually lower the defibrillation threshold (DFT), which can provide a unique beneficial effect on ICD function. The Vaughan-Williams Class III antiarrhythmic agents (dofetilide, azimilide, and sotalol) appear to decrease the energy requirements for defibrillation.^{24–26} Although the authors have not routinely used, nor do they recommend antiarrhythmic drug therapy use for the sole purpose of lowering DFT, this potential effect may be of partic-

ular benefit in patients with marginal defibrillation safety margins.

Effectiveness of Antiarrhythmic Drugs for Preventing ICD Shocks

Despite the widespread use of antiarrhythmic drug therapy in patients with an existing ICD, there are only a few studies documenting the efficacy of such therapy in this patient population. Pacifico et al.²⁷ conducted the first well-designed trial examining the effect of pharmacologic therapy on ICD shock frequency. In this multicenter trial, patients were randomly assigned to double-blinded treatment with 160–320 mg of D, L-sotalol per day ($n = 151$) or a matching placebo ($n = 151$). Compared to placebo, treatment with sotalol was associated with a 48% ($P < 0.001$) risk reduction in death from all causes or delivery of first shock for any reason, and a 64% ($P = 0.004$) risk reduction in death from all causes or delivery of a first inappropriate shock. In this study, sotalol was also found to reduce the mean frequency of delivered shocks due to any cause as compared to placebo ($P = 0.008$).²⁷ In another study, Kuhlkamp et al.²⁸ showed that D, L-sotalol significantly reduced the recurrence of sustained VT in comparison to patients with only an ICD and no additional pharmacologic therapy. O'Toole et al.,²⁹ in a similarly designed multicenter, double-blinded placebo-controlled trial of 174 patients with a prior ICD showed that the class III agent, dofetilide, prolonged the median time to all cause mortality and first appropriate shock. In a recently published double-blinded, placebo-controlled pilot study, azimilide (class III agent) reduced the frequency of appropriate ICD therapies by 69% compared with placebo (hazard ratio 0.31, $P = 0.0001$).³⁰

The antiarrhythmic effects of β -adrenergic blocking agents (Vaughan Williams Class II) are often overlooked in this patient population. The β -adrenergic blocking agents are efficacious antiarrhythmic drug therapies with a favorable side-effect profile that should be instituted in all ICD patients with coronary heart disease and/or congestive heart failure. One prospective randomized trial of 100 patients with an existing ICD compared the effects of metoprolol and D, L-sotalol on the rate of arrhythmia recurrence and total mortality. In this trial there were no significant differences between the two study groups with regards to the recurrence of VF/VT, total mortality, and event-free survival. The authors concluded that metoprolol is as efficacious as sotalol in preventing VT/VF recurrence in patients with a prior ICD.³¹ The ongoing Optimal Pharmacological Therapy in Implantable Cardioverter (OPTIC) study is being conducted to determine if combined treatment

with amiodarone and β -blockers or sotalol alone will reduce the occurrence of ICD shocks compared to treatment with β -blockers alone. In this study patients are being randomized to one of the three treatment arms: (1) β -blockers alone, (2) sotalol, or (3) amiodarone and β -blockers (carvedolol, bisoprolol, or metoprolol) and all patients will receive a dual chamber ICD. The primary outcome measure is the time to first ICD shock, either appropriate or inappropriate.³²

Finally, a recent follow-up study of the ICD arm from the AVID trial showed that there were 1.4 ± 3.7 fewer ICD therapy events ($P = 0.005$) after addition of an antiarrhythmic drug, which were predominantly accounted for by a reduction in delivered shocks rather than antitachycardia pacing therapies. In this follow-up study, amiodarone was the most commonly used antiarrhythmic agent and was used by 42% of the patients with a prior ICD. Overall, the arrhythmia event rate was reduced from 90% to 64% ($P < 0.001$) in the crossover group after the institution of pharmacologic therapy.⁴

Adverse Antiarrhythmic Pharmacologic and Device Interactions (Table II)

Increase in DFT

The DFT is defined as the lowest delivered energy that will convert VF to a supraventricular rhythm. An increase in DFT may lead to failure of device therapy, and as a result may have severe life-threatening consequences. Discordant results have been reported in several studies investigating the effect of antiarrhythmic agents on DFT. As a result, it is difficult to arrive at a definite conclusion with regards to the effect of antiarrhythmic drugs on ICD DFT. Nonetheless, below is a summary of the known effects.

Class IA antiarrhythmic agents have been shown to have inconsistent effects on the DFT in various studies. In a few canine studies quinidine was found to be associated with an increase in the DFT³³ whereas, another experimental study showed that quinidine had little effect on DFT.³⁴ Data with regards to other class IA agents, specifically procainamide and disopyramide, has shown that these drugs do not appear to significantly affect the DFT.^{34,35} Of the class IB antiarrhythmic agents, lidocaine is the most extensively studied and has frequently been shown to be associated with an increase in DFT.^{35,36} With regards to another class IB agent, mexiletine, a preliminary study by Senatore et al.³⁷ revealed that in patients with an existing ICD mexiletine increases DFT more often than amiodarone. The effect of the class IC agents has also been investigated and flecainide has not been associated with an increase in DFT in several animal studies.³⁸ However, one study, where the investigators used an anesthetized dog model, demonstrated a significant increase in DFT with flecainide.³⁹ Moricizine, another class IC agent, has also been associated with an increase in the DFT in one animal study. The combination of moricizine with lidocaine resulted in a synergistic rise in DFT.^{40,41} In one human study, Stevens et al.⁴² concluded that the class IC agent propafenone was not associated with any significant affect on DFT in patients with a prior ICD.

The other antiarrhythmic drug often associated with elevations in the DFT is amiodarone. This drug appears to have a less consistent effect on DFT,^{43,44} but in selected individuals may be associated with a potentially life-threatening increase in DFT when administered chronically (Fig. 3).^{45,46} The Low Energy Safety Study (LESS) assessed the efficacy and the safety of

Table II.

Potential Adverse Effects of Combining Antiarrhythmic Drugs with ICD Therapy

- Increase in the defibrillation and/or pacing threshold leading to device inefficacy.
- Prolongation of the tachycardia cycle length below the device lower rate limit or enhancing rate instability of VT leading to inappropriate withholding of device therapy.
- Proarrhythmic effects resulting in more ventricular arrhythmia episodes and delivered therapies.
- Organization of atrial fibrillation to atrial flutter with rapid ventricular conduction or enhancing AV nodal conduction during atrial fibrillation resulting in inappropriate device therapy.
- Creation of bradyarrhythmias or delayed conduction resulting in increased bradypacing therapy
 - Increase device usage and battery depletion
 - Increased incidence of pacemaker syndrome
 - Enhanced LV dyssynchrony with the need for RV apical pacing and the precipitation of heart failure

AV = atrioventricular; ICD = implantable cardioverter defibrillator; LV = left ventricular; RV = right ventricular; VT = ventricular tachycardia.

threshold.⁴⁹ Drugs that inhibit sodium channel conduction also may produce rate dependent elevations in the pacing threshold and these elevations may be quite dramatic, particularly for the class IC agents which may then render antitachycardia pacing ineffective.⁵⁰ This phenomenon, known as *use-dependent block*, is central for the antiarrhythmic action of this class of drugs whereby the magnitude of ion channel blockade increases with repetitive depolarizations.⁵¹ Therefore, an increase in the frequency dependent pacing threshold must be taken into consideration when one is programming the antitachycardia pacing output. For this reason the authors suggest that the output for all antitachycardia pacing therapies be programmed to the highest available energy output to provide a safety margin that guarantees capture during treatment of VT.

Typically, it is assumed that by reducing the VT rate the arrhythmia is rendered more amenable to termination by antitachycardia pacing by providing a longer diastolic period, which allows for more antidromic penetration into the tachycardia circuit. For the vast majority of patients the preceding paradigm will largely hold true, however, this is not always the case for every patient. In a few selected patients, the authors found that the efficacy of antitachycardia pacing may actually be paradoxically lower with slower tachycardia rates. They presumed this to result from alterations in the local conduction and refractoriness, which may affect the timing of a critically introduced train of pulses. Therefore, they recommend that the efficacy of all antitachycardia pacing therapies be tested during noninvasive programmed stimulation in patients treated with an antiarrhythmic drug who have documented VT to ensure appropriate device programming. Amiodarone, a drug which possesses electrophysiological effects common to all four Vaughan-Williams classes, may also be associated with increased pacing threshold (Table III).

Prevention of Accurate Arrhythmia Recognition

As mentioned above, it is a well-recognized phenomenon that antiarrhythmic drugs will slow the rate of any given VT. Although this is primarily a beneficial effect due to improvements in hemodynamic tolerance, slowing the rate of a VT below the lower rate cutoff an antitachycardia device may produce disastrous consequences (Fig. 4). In many situations, the degree of slowing of the VT can be anticipated for the individual antiarrhythmic agent used, however, the observed clinical response may sometimes be different than is expected.^{52,53} In addition, the late developing effects on heart rate with an antiarrhythmic drug that

Table III.
General Effects of Antiarrhythmic Agents on DFT and Pacing Thresholds

Vaughan-Williams Classification	Effect on DFT	Effect on Pacing Threshold
IA	+/-	↑
IB	↑	↑
IC	+/-	↑
II	0	0
III	↓(↑ w/amiodarone)	0
IV	0	0

↑ = evidence supports an increase; ↓ = evidence supports a decrease; 0 = evidence supports no significant effect; +/- = conflicting evidence; DFT = detibrillation threshold.

have complex metabolism, like amiodarone, must also be anticipated.

Proarrhythmic Effects Leading to Increased Device-Based Antitachycardia Therapy

The proarrhythmic effects of antiarrhythmic drugs are well known and may lead to more frequent and malignant arrhythmias requiring increased ICD intervention. It must be recognized that because of the complex electrophysiological milieu associated with ventricular arrhythmogenesis, an effective antiarrhythmic drug in one patient may be proarrhythmic in another. Selection of drug therapy for arrhythmia control is empiric and a proarrhythmic risk must be considered when instituting antiarrhythmic drug therapies. Occasionally, certain antiarrhythmic agents which block repolarization currents may induce QT interval prolongation and pause dependent polymorphic VT.⁹ Proarrhythmia by potentiating a more rapid rate with atrial arrhythmias must also be considered. Vaughan Williams Class I agents, in addition to amiodarone, slow atrial conduction velocity and may consequently lead to the organization of atrial fibrillation into atrial flutter with a relatively long atrial cycle length. This may subsequently result with catecholamine potentiation in atrial flutter with 1:1 atrioventricular conduction and rapid ventricular rate-response. Such a rapid, regular response to atrial flutter is difficult for the antitachycardia device to correctly identify as a supra-VT. Ventricular antitachycardia pacing will be ineffective and shock therapy is often delivered in these cases. Also, the vagolytic action that some pharmacologic agents, like quinidine, have on atrioventricular (AV) nodal conduction may produce a more

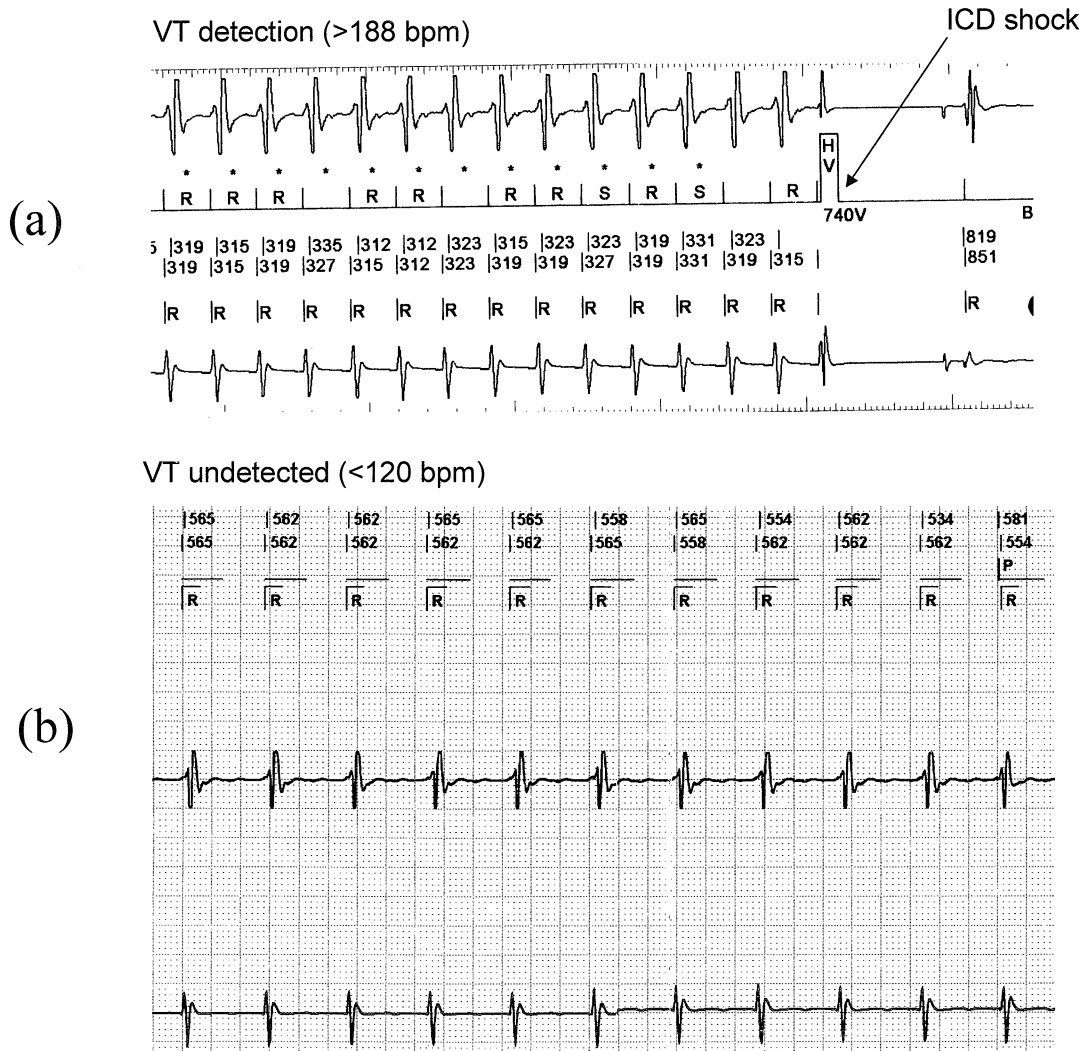


Figure 4. Amiodarone therapy slowing the ventricular tachycardia (VT) rate below the device VT detection zone. (A) Prior to the initiation of amiodarone therapy, the patient had VT at a rate of about 200 beats/min, which the device appropriately detects and treats with a 740-V shock. (B) After initiation of amiodarone therapy for the prevention of appropriate shocks by the device, the patient had ventricular tachycardia at a rate of 110 beats/min that fell below the VT detection zone. The device failed to detect or treat this arrhythmia. In all panels the top tracing is the device interpretation markers, the middle tracing is the atrial electrogram, and the bottom tracing is the ventricular electrogram from the sensing bipole. Note that the morphology of the ventricular electrogram is identical in both panels (A and B) which helps to identify the slower rhythm in panel B as VT. This patient subsequently underwent catheter ablative therapy to eliminate slow VT and permit continuation of amiodarone therapy. ICD = implantable cardioverter defibrillator.

rapid, and thereby more regular ventricular response to atrial fibrillation that may also lead to the delivery of inappropriate device therapy (Fig. 5). Increased ventricular pacing and shock device therapy for supraventricular arrhythmias may not only produce morbidity from multiple shocks, but may also occasionally precipitate more rapid ventricular arrhythmias with adverse hemodynamic effects.⁵⁴ Finally, sodium channel-blocking drugs (especially the potent class IC agents) increase

QRS and sensed electrogram duration, which may lead to rhythm misclassification by some devices with the delivery of inappropriate therapy during supraventricular arrhythmias if morphology sensing criteria are used.⁵⁵

Precipitation of Bradyarrhythmias

Drug induced slowing of the sinus rate or alteration of AV conduction is a frequently overlooked adverse consequence of antiarrhythmic

complications of ICD therapy. Overall, atrial fibrillation with a rapid ventricular response is the most frequent cause of inappropriately delivered ICD therapy.⁵⁶ The stability criterion was developed for use in antitachycardia devices to help differentiation VT (stable ventricular rates) from atrial fibrillation with a rapid ventricular response (irregular ventricular rates). Vaughan Williams Class IC antiarrhythmia agents may enhance rhythm variability, which then prevents the device from meeting the programmed stability criteria and produce a critical delay in VT detection. The likely mechanism for this phenomenon is alteration of myocardial refractoriness and conduction velocity by the drug which can change the directionality of the excitation wavefront within the reentry circuit and enhance variability.⁵⁷ To avoid under detection of ventricular arrhythmias in patients treated with an antiarrhythmic drugs, the stability criterion was programmed with the onset and sustained rate duration features as well, and the stability criterion is not programmed "On" for rapid VTs or poorly tolerated arrhythmias where a significant delay in detection could have adverse clinical consequences. For these reasons the authors suggest that careful testing of device function should be performed in patients treated with an antiarrhythmic agent before discharge or with a change in device detection criteria.⁵⁷

Selection of Specific Antiarrhythmic Drug

Although the basic electrophysiological effects of each of the clinically approved antiarrhythmic drugs are well known, the selection of which agent to use for the treatment of ventricular arrhythmias still remains largely empiric. Any of the approved antiarrhythmic agents can be used to suppress and treat ventricular arrhythmias, and with the exception of the class IB agents, they can all effectively suppress frequent supra-VTs. The studies quoted in this article support the use of sotalol, dofetilide, or amiodarone in patients with a prior ICD. The potential adverse side-effects associated with antiarrhythmic therapy, including bradycardia or torsades de pointes, are less of a concern in patients with an ICD which has backup pacing and shocking capabilities. In addition, the availability of a backup device therapy permits the use of low dose antiarrhythmic therapy to minimize dose dependent side-effects.

Among the individual antiarrhythmic agents, the authors noted a dramatic decrease in the use of class I antiarrhythmic agents over the past 10 years, while the proportion of patients treated with a class III agent has steadily increased over the past decade. Amiodarone is currently the

most common antiarrhythmic drug therapy used in combination with an ICD. The popularity of amiodarone use in this patient population is likely due to its overall efficacy for atrial and ventricular arrhythmias, its ease of use (once a day dosing) its low proarrhythmic risk, and its lack of adverse hemodynamic effects in patients with structural heart disease. At the present time, nearly two thirds of the patients at the authors' institute who are undergoing combination device-based and pharmacologic therapies are being treated with amiodarone (Fig. 6). As noted before, amiodarone was also the most common agent selected for treating patients enrolled in the AVID trial. Importantly, it is not clear whether the present trend towards a decrease in class I antiarrhythmic agent use in patients with an existing ICD has implications related to efficacy or whether it merely reflects the overall practice of avoid these agents in patients with structural heart disease. Because the class I agents have potentially beneficial antiarrhythmic effects, it is important that the efficacy and tolerance of these drugs be evaluated more systematically in patients with an ICD before they are automatically relegated to the bottom rung of the drug selection ladder. The use of class I antiarrhythmic agents may be an especially important consideration in younger patients with an ICD where end-organ toxicity associated with long-term amiodarone therapy is a significant concern.

■ Class I Agents ■ Sotalol □ Amiodarone

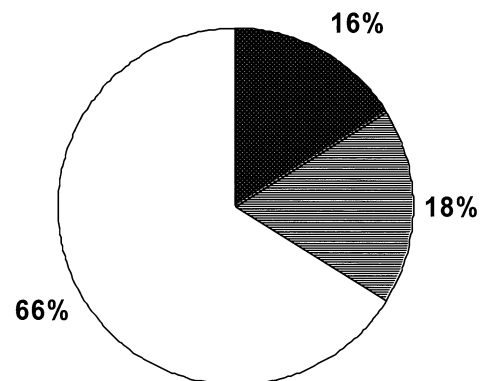


Figure 6. Antiarrhythmic agents used to treat patients with an ICD at the University of Pennsylvania Health System in the year 2000. Of the 306 patients with an ICD that was followed at the center during the year 2000, 112 (37%) were also treated with an antiarrhythmic agent. Of the patients treated with an ICD and an antiarrhythmic agent, about two of three were receiving the drug amiodarone. ICD = implantable cardioverter defibrillator.

Maintaining Efficacy and Safety of Device-Based Therapy in Combination with Pharmacologic Therapy

To minimize the adverse consequences of antiarrhythmic drug therapy in patients with an ICD, a systematic approach to the initiation of such therapy is imperative.^{58,59} Potential adverse side-effects on baseline sinus rate, AV nodal conduction, supra-VT rate and rhythm, VT rate, and elevations in the pacing and DFT should be anticipated and rigorously assessed in all patients. For this reason, with institution of a new antiarrhythmic agent or change in drug regimen, the authors strongly recommend detailed noninvasive electrophysiological testing. The testing should include documentation of the pacing thresholds, the device's efficacy for defibrillation with an adequate safety margin and its ability to treat VT with overdrive pacing and cardioversion. The authors feel that careful programming of the device based on the documented and anticipated effects of antiarrhythmic drug therapy should become the standard of care for all patients.

Summary

Device-based therapy has become the treatment of choice in the majority of patients for primary and secondary prevention of lethal ventricular arrhythmias with continually expanding indications for their use.⁵ However, despite the high efficacy of device-based therapy, many patients with an ICD will still require adjuvant pharmacologic therapy for optimal management of their arrhythmias. To date, only a few randomized studies have evaluated the effects of antiarrhythmic agents for optimizing ICD therapy. While sotalol has been shown to effectively reduce the frequency of ICD shocks, many of the patients who require concomitant antiarrhythmic drug therapy to prevent ICD shocks have poor ventricular function and low cardiac output and cannot tolerate the hemodynamic effects of sotalol.²⁷ A prelimi-

nary pilot study has suggested that azimilide, a class III agent, is effective in reducing the number ICD shocks in patients with reduced left ventricular systolic function. In addition, this drug was well tolerated and did not seem to have significant effects on DFT. The results of this pilot study were intriguing but still need to be confirmed in a large patient cohort and The Shock Inhibition with Azimilide (SHEILD) study is currently in progress to confirm these results.³⁰ The OPTIC is another randomized study in progress to evaluate the effectiveness of antiarrhythmic drugs for preventing shocks in patients with an ICD. The OPTIC trial proposed that combined treatment with amiodarone and β -blockers or sotalol alone would reduce the occurrence of ICD shocks compared to treatment with a β -blocker alone.

Importantly, the management of patients with arrhythmia disorders and left ventricular dysfunction is constantly evolving. For example, the recent approval of biventricular ICDs, along with preliminary data suggesting these devices may reduce recurrence of VT, and will perhaps reduce the need for concomitant drug therapy in selected patients.

In closing, the authors feel that the state of current practice dictates that the management of ventricular arrhythmias should include the ability to recognize the indications and benefits of combining device-based and pharmacologic treatments. Just as important, a complete understanding of the potential pitfalls of hybrid therapy and how to avoid them is required for optimal patient management. Because antiarrhythmic drug therapy may affect ICD function in a variety of ways as described, the authors strongly feel that the appropriateness of device sensing parameters and the efficacy of programmed therapy should be routinely assessed in most patients after the institution or modification of pharmacologic treatment.

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