p Catheter Ablation be the Preferred Therapy for Reducing ICD Shocks?

Ventricular Tachycardia Ablation Versus Drugs for Preventing ICD Shocks

Role of Adjuvant Antiarrhythmic Drug Therapy

Chinmay Patel, MD; Gan-Xin Yan, MD, PhD; Dusan Kocovic, MD; Peter R. Kowey, MD, FAHA

In 1980, Mirowski et al1 implanted the first implantable cardioverter-defibrillator (ICD) in a young female with recurrent ventricular fibrillation and provided an innovative approach to aborted sudden cardiac death (SCD). Although the ICD was considered a treatment of last resort during that incipient stage, subsequent years have witnessed prolific expansion of indications for ICD implantation.2 Several large-scale clinical trials have demonstrated its efficacy for both primary and secondary prevention of SCD in patients with ischemic and nonischemic cardiomyopathy.3,4 ICD therapy in such high-risk patients has been shown to improve survival compared with conventional antiarrhythmic drug therapy alone.3,4 The number of ICD implantations has increased significantly in the last decade, with a concurrent decrease in the use of stand-alone antiarrhythmic drugs for ventricular indications.5–7 Current ICDs have sophisticated programming capabilities, atrial and bipolar leads, and are able to deliver antitachycardia pacing algorithms (ATP) in addition to defibrillating shocks.

Response by Kuck on p 712

ICD Therapy: Life Extension and Quality of Life

Typically, patients who receive ICDs are at high risk for recurrent arrhythmia; hence, most patients receive 1 or more ICD therapies for spontaneous arrhythmias after implantation.9 Despite the technological evolution of ICD systems, more than 20% of shocks are due to supraventricular arrhythmia and hence are inappropriate.8–10 The ICD uses ATP or defibrillating shocks to terminate episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF). Although the ICD aborts VT/VF, many patients continue to have symptoms such as dizziness, palpitations, nervousness, flushing, or syncope before receiving an ICD shock.11 When the shock is finally delivered, it is physically and emotionally painful and so noxious that 23% of patients dread shocks and 5% of patients prefer to do without an ICD and “take their chances.”12 A significant prevalence of sadness, depression, and even anxiety disorders have been reported after implantation of an ICD, and these symptoms are more pronounced in those who receive frequent ICD discharges.13,14 Clearly, ICD shocks lead to poor quality of life and adverse psychological outcomes in patients and their families.

Potential Benefits of Combining Antiarrhythmic Drugs With ICD Therapy

Although ICD implantation has been shown to be superior to conventional antiarrhythmic drugs in reducing SCD, adjuvant...
use of antiarrhythmic drugs in some patients sometimes becomes necessary and may be beneficial. The usefulness of this approach is reflected in the fact that upward of 70% of patients with an ICD receive adjuvant antiarrhythmic drug therapy, even though there is no antiarrhythmic drug formally approved for this indication.\textsuperscript{15,16} Evidence regarding the importance of antiarrhythmic drugs in some patients sometimes becomes necessary and may be beneficial. The usefulness of this approach is reflected in the fact that upward of 70% of patients with an ICD receive adjuvant antiarrhythmic drug therapy, even though there is no antiarrhythmic drug formally approved for this indication.\textsuperscript{15,16} Evidence regarding the importance of antiarrhythmic drugs in the treatment of ICD-implanted patients comes from the device arm of the AVID (Antiarrhythmic versus Implantable Defibrillator) trial.\textsuperscript{17} About 18% patients in the ICD arm of the AVID trial had to be started on adjuvant antiarrhythmic drug therapy (amiodarone, 42%; sotalol, 21%; and mexiletine, 20%) to reduce frequent ICD shocks and to prevent recurrent ventricular arrhythmias. Adjuvant antiarrhythmic drug therapy in these crossover patients increased the time to first event by almost 7 months and reduced the 1-year arrhythmia event rate from 90% to 64%.

The principle advantages of adjuvant antiarrhythmic drug therapy are summarized in Table 1. Most importantly, antiarrhythmic drugs prevent frequent paroxysms of ventricular and atrial tachyarrhythmias, thereby reducing both appropriate and inappropriate ICD shocks. Additionally, most antiarrhythmic drugs tend to prolong the tachycardia cycle length to render the tachycardia hemodynamically stable and amenable to termination with ATP.\textsuperscript{18} Also, it has been suggested that \(\approx 2\%\) of episodes of VT are refractory to appropriate defibrillator therapy.\textsuperscript{19} Antiarrhythmic drugs in such cases may serve as an additional defense against SCD. Reduced ICD interventions have also been shown to decrease emergency department visits and decrease rates of hospitalization.\textsuperscript{20,21} A decrease in the number of ICD discharges also prolongs the battery life of the device.\textsuperscript{22}

Antiarrhythmic drugs are of particular importance in the management of electrical storm. Electrical storm, defined as 3 or more episodes of destabilizing VT/VF occurring in a 24-hour period, develops in \(\approx 10\%\) to 30% patients with ICD and is associated with increased morbidity and a higher 3-month mortality.\textsuperscript{23–25} Prompt hospitalization with reversal of precipitating factors and optimization of \(\beta\)-blocker therapy is recommended in such cases. Many patients require addition of intravenous amiodarone followed by oral maintenance dosing to abort and prevent recurrent ventricular arrhythmia.\textsuperscript{23,26} Such a strategy results in long-term outcomes similar to those seen in ICD patients without electrical storm.\textsuperscript{23,26} Recent evidence suggests that the investigational agent azimilide may also be effective in prevention and treatment of electrical storm.\textsuperscript{27} Additionally, some antiarrhythmic drugs may reduce the defibrillation threshold (DFT) and facilitate defibrillation of VT/VF, as discussed in later sections of this report.

Table 1. Benefits and Pitfalls of Adjuvant Antiarrhythmic Drug Therapy in ICD Patients

<table>
<thead>
<tr>
<th>Pros</th>
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<tbody>
<tr>
<td>Decrease in appropriate ICD shocks due to suppression of recurrent VT/VF</td>
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<tr>
<td>Decrease in inappropriate ICD shocks due to reduced frequency and better rate control of supraventricular rhythm</td>
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<tr>
<td>Slowing of tachycardia leading to improved hemodynamic tolerance</td>
<td></td>
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<tr>
<td>Slowing of rate of tachycardia facilitating successful termination by ATP</td>
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<tr>
<td>Prolongation of ICD battery life</td>
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<tr>
<td>Decrease in frequency of symptomatic non-sustained ventricular arrhythmias</td>
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<tr>
<td>Prevention and better treatment of electrical storm</td>
<td></td>
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<tr>
<td>Improved quality of life and sense of well-being</td>
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<tr>
<td>Reduced defibrillation threshold facilitating easier defibrillation</td>
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<tr>
<td>Improved control of maximal sinus rate</td>
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<tr>
<td>Reduced rate of recurrent ICD related hospitalizations</td>
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<tr>
<td><strong>Cons</strong></td>
<td></td>
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<tr>
<td>Interference in ICD function due to</td>
<td></td>
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<tr>
<td>Increase in defibrillation threshold</td>
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<tr>
<td>Increase in pacing threshold</td>
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<tr>
<td>Interference in accurate arrhythmia detection due to</td>
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<tr>
<td>Slowing of rate of ventricular tachycardia</td>
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<td>Decrease in amplitude of electrocardiogram interfering with sensing</td>
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<td>Limiting effectiveness of rate stability criterion</td>
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<tr>
<td>Adverse effects</td>
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<td>Cardiac</td>
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<td>Bradycardia</td>
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<tr>
<td>Torsades de pointes</td>
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<tr>
<td>Impairment of myocardial function</td>
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<td>Extracardiac toxicity</td>
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</table>

Clinical Trials Supporting the Efficacy of Adjuvant Antiarrhythmic Drug Therapy

Several large-scale clinical trials have evaluated and compared the efficacy of various antiarrhythmic drugs as adjuvant therapy to prevent ICD shocks, as listed in Table 2.\textsuperscript{20,28–33} The majority of patients enrolled in these trials received ICD for secondary prevention of SCD or documented episode of VT/VF. Their principle findings are described below.

Sotalol

Pacifico et al\textsuperscript{28} first demonstrated the efficacy of oral sotalol for the prevention of both appropriate and inappropriate ICD shocks. In this prospective multicenter trial, 302 patients with ICDs were randomly assigned to receive either \(d,l\)-sotalol or matching placebo and followed for 12 months. Treatment with sotalol led to a reduction of the primary end point of all-cause death or all-cause ICD shocks (hazard ratio [HR], 0.52%; \(P<0.001\); Figure 1), all-cause death or first appropriate shock (HR, 0.56%; \(P=0.007\)), and all-cause death or delivery of first inappropriate shock (HR, 0.36; \(P=0.007\)), irrespective of left ventricular ejection fraction or concomitant use of \(\beta\)-blockers. The mean frequency of all-cause shock was 1.43\(\pm\)3.53 in the sotalol group compared with 3.89\(\pm\)10.65 in control group. In \(\approx 27\%\) of patients in the sotalol group, treatment was stopped early because of adverse
events, most commonly related to β-receptor blocking effects, and only 1 episode of torsades de pointes (TdP) was reported.

In a smaller study, Kuhlkamp et al demonstrated that adjuvant treatment with sotalol in ICD patients led to a significant reduction in recurrent VT/VF and ICD treatment. During 1 year of follow-up, 25.5% patients in the ICD-only treatment arm required adjuvant antiarrhythmic drug therapy for suppression of recurrent VT/VF or supraventricular arrhythmias, similar to the results in the ICD arm of AVID. Adrenergic Blockers

In the study by Pacifico et al, treatment with β-blockers had no effects on event-free survival. In contrast, a study by Seidl et al demonstrated efficacy of β-blockers in a small prospective study of 70 patients with an ICD who were randomly assigned to either metoprolol or d,l-sotalol. The survival probability estimated for reaching a combined end point of symptomatic recurrence of fast VT or VF or death was significantly better at 1 and 2 years in the metoprolol group (83% and 74%, respectively) as compared with the sotalol group (47% and 38%, respectively, \( P = 0.004 \)). ICD interventions in the form of ATP and shocks were significantly lower in the metoprolol arm compared with the sotalol arm. On the other hand, in a similar study by Kettering et al involving 100 patients with an ICD, β-blockers, and sotalol were equally effective in reducing the incidence of VT/VF and ICD interventions. Similar efficacy of β-blockers was reported by Brodine et al in a post hoc analysis of the MADIT-II trial. In this retrospective analysis, the patient

### Table 2. Clinical Trials Summarizing Benefits of Adjuvant Antiarrhythmic Drug Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug/Dose</th>
<th>No. per Group</th>
<th>Follow-Up</th>
<th>Primary End Point</th>
<th>Secondary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacifico et al</td>
<td>Sotalol (207 ± 55 mg) vs placebo</td>
<td>151</td>
<td>12 mo</td>
<td>All-cause death or all-cause ICD shock:</td>
<td>Mean frequency of shocks due to any cause:</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Sotalol: 44% (HR: 0.52)</td>
<td>Sotalol: 1.43 ± 3.53*</td>
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<td></td>
<td>Placebo: 56%</td>
<td>Placebo: 3.39 ± 10.65</td>
</tr>
<tr>
<td>Kuhlkamp et al</td>
<td>Sotalol (80 to 400 mg) vs placebo</td>
<td>~46</td>
<td>12 mo</td>
<td>Recurrence of VT/VF:</td>
<td>Total mortality:</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Sotalol: 32.6%*</td>
<td>Same across the groups</td>
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<td></td>
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<td></td>
<td></td>
<td>Placebo: 53.2%</td>
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<tr>
<td>Seidl et al</td>
<td>Metoprolol (104 ± 37 mg) vs sotalol (242 ± 109 mg)</td>
<td>35</td>
<td>26 ± 16 mo</td>
<td>Appropriate ICD therapy:</td>
<td>Total mortality:</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>VT treated by ATP:</td>
<td>Metoprolol: 6 deaths</td>
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<td></td>
<td></td>
<td>Metoprolol: 20%*</td>
<td>Sotalol: 6 deaths</td>
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<td></td>
<td>Sotalol: 49%</td>
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<td>Fast VT/VF treated by ICD shocks:</td>
<td>Actuarial survival rate:</td>
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<td></td>
<td>Metoprolol: 20%*</td>
<td>Not different between the 2 groups</td>
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<td></td>
<td>Sotalol: 54%</td>
<td></td>
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<tr>
<td>Kettering et al</td>
<td>Metoprolol (108 ± 44 mg) vs sotalol (319 ± 91 mg)</td>
<td>50</td>
<td>727 d</td>
<td>Recurrent VT/VF requiring ICD therapy:</td>
<td>Total mortality:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metoprolol: 66%</td>
<td>Metoprolol: 8 deaths</td>
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<td></td>
<td></td>
<td>Sotalol: 60%</td>
<td>Sotalol: 6 deaths</td>
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<td>Event-free survival not different between groups</td>
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<tr>
<td>Singer et al</td>
<td>Azimilide 35, 75, or 125 mg vs placebo</td>
<td>~35–46</td>
<td>374 d</td>
<td>Frequency of appropriate ICD shocks and ATP:</td>
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<td>Placebo: 36</td>
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<td>35 mg AZ: 10*</td>
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<td>75 mg AZ: 12*</td>
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<td>125 mg AZ: 9* per patient-year (HR: 0.31)</td>
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<tr>
<td>Dorian et al</td>
<td>Azimilide 75, 125 mg vs placebo</td>
<td>~199–214</td>
<td>1 y</td>
<td>All-cause shock and ATP:</td>
<td>Appropriate ICD therapy:</td>
</tr>
<tr>
<td>SHIELD</td>
<td></td>
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<td>75 mg AZ: HR=0.43*</td>
<td>75 mg AZ: HR=0.52*</td>
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<td>125 mg AZ: HR=0.53* as compared with placebo</td>
<td>125 mg AZ: HR=0.38* as compared with placebo</td>
</tr>
<tr>
<td>Connolly et al</td>
<td>β-blocker vs sotalol vs amiodarone plus β-blocker</td>
<td>~134–138</td>
<td>1 y</td>
<td>All-cause ICD shock:</td>
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<tr>
<td>OPTIC</td>
<td></td>
<td></td>
<td></td>
<td>β-blocker: 38.5%</td>
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<td></td>
<td>Sotalol: 24.3%</td>
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<td></td>
<td>Amiodarone plus β-blocker: 10.3%* (HR: 0.27 vs β-blocker, HR: 0.43 vs sotalol)</td>
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</tbody>
</table>

AZ indicates azimilide.

*Significant \( P \) value.
receiving higher doses of β-blockers had a significant reduction in risk of recurrent VT/VF requiring ICD therapy as compared with patients not receiving β-blockers (HR, 0.48; $P=0.02$).

Azimilide

Azimilide is a novel class III (Vaughan-Williams) drug that blocks both the rapid and slow components of the delayed rectifier cardiac potassium current and is effective in a variety of supraventricular arrhythmias. It was shown early on to suppress both atrial and ventricular arrhythmias with preserved or even superior efficacy in patients with severe left ventricular dysfunction.

Singer et al first tested azimilide in a dose-range pilot study of 172 ICD patients. These patients were randomly assigned to receive placebo or azimilide (35 mg, 75 mg, or 125 mg). At a mean follow-up of 257±158 days, azimilide significantly reduced the frequency of appropriate ICD therapies (shocks and ATPs) at all administered doses compared with placebo (HR, 0.31; $P=0.0001$) without any effects on left ventricular function, resting heart rate, defibrillation, or pacing thresholds. The incidence of ICD therapies per patient-year among the placebo group was 36% compared with 10%, 12%, and 9% among 35 mg, 75 mg, and 125 mg azimilide dose groups, respectively.

The efficacy of azimilide was further investigated by Dorian et al in a large prospective double-blind trial called SHIELD (Shock Inhibition Evaluation With Azimilide), in which 75 mg and 125 mg doses of azimilide were evaluated in 633 ICD recipients. At a median follow-up of 367 days, all-cause shocks plus symptomatic arrhythmia terminated by ATP were significantly reduced by both 75 mg and 125 mg of azimilide (HR, 0.43 and 0.53; $P=0.0006$ and $P=0.0053$, respectively; Figure 2). There was no statistically significant difference between the 2 doses with respect to risk reduction, and there was a trend toward a reduction in the primary endpoint of all-cause shock alone with both doses of azimilide.

The secondary endpoint of all appropriate ICD therapies (shocks or ATPs) was reduced by both 75 and 125 mg/d azimilide (HR, 0.52 and 0.38; $P=0.017$ and $P=0.0004$, respectively, Figure 2), with a trend toward a larger effect at the 125 mg dose. Additional analyses revealed that the incidence of all ICD interventions was reduced from 25.1 events per patient-year on placebo to 17.1 and 9.6 events per patient-year on 75 and 125 mg of azimilide. All-cause shocks were reduced from 4 shocks per patient-year in the placebo group to 2.8 and 3.3 shocks per patient-year in the 75 and 125 mg azimilide groups. About 86% of patients in SHIELD were receiving concomitant β-blocker therapy, suggesting that the benefits of azimilide were over and above traditional therapy.

Azimilide also increased the interevent interval as compared with the control group, suggesting its benefit in the treatment of electrical storm. This benefit was confirmed by Hohnloser et al in a subsequent analysis of SHIELD data. During 1 year of follow-up, 23% of SHIELD patients had at
least 1 episode of electrical storm that led to an almost 10-fold increase in hospitalization rates as compared with patients without VT/VF.\textsuperscript{27} Treatment with 75 mg and 125 mg/d azimilide reduced the risk of electrical storm by 37\% and 55\%, respectively, as compared with placebo. These beneficial effects of azimilide translated into reduced emergency department visits and hospitalizations.\textsuperscript{21}

Azimilide was very well tolerated, with the overall incidence of adverse events not different compared with placebo.\textsuperscript{20,32,33} Early discontinuation for any reason occurred in 40\% of placebo patients versus 36\% and 35\% patients receiving 75 mg and 125 mg azimilide in SHIELD.\textsuperscript{20} Although azimilide caused dose-dependent prolongation of the QT interval, TdP was reported in 1 patient taking placebo, 2 patients receiving 75 mg of azimilide, and 3 patients receiving 125 mg of azimilide, all without sequelae.\textsuperscript{20} One patient had severe but reversible neutropenia with 75 mg azimilide.\textsuperscript{20} In context of the above data, azimilide is the first-ever drug submitted to the Food and Drug Administration and currently is under review to be used for this indication.

**Amiodarone**

The OPTIC (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients) study investigated and compared the efficacy of \(\beta\)-blocker, sotalol, and \(\beta\)-blocker plus amiodarone in the prevention of ICD shocks.\textsuperscript{33} The OPTIC investigators randomly assigned 412 patients with an ICD and followed them for 1 year. Patients in the 2 active treatment groups had a reduced risk of shock of 56\% compared with \(\beta\)-blocker alone (HR, 0.44; \(P<0.001\)). Also, amiodarone plus \(\beta\)-blocker was more effective than \(\beta\)-blocker alone (HR, 0.27; \(P<0.001\)) or sotalol (HR, 0.43; \(P=0.02\)) in preventing both appropriate and inappropriate ICD shocks (Figure 3). There was a trend toward better efficacy of sotalol as compared with \(\beta\)-blocker alone in preventing ICD shocks, but the results did not reach statistical significance. Mortality rate was not significantly different among the 3 groups, and no cases of TdP were reported. Rates of study drug discontinuation at 1 year were 18.2\% for the amiodarone group, 23.5\% for the sotalol group, and 5.3\% for the \(\beta\)-blocker–alone group. Adverse pulmonary, thyroid, and bradycardic events were more common with amiodarone treatment.

**Other Drugs**

Similar to its parent drug amiodarone, dronedarone was also effective in reducing the rate of appropriate ICD intervention during a 30-day follow-up in a small study.\textsuperscript{36} Dofetilide, a pure class III blocker, was shown to be effective in increasing the median time to first all-cause ICD shocks in a study by O’Toole et al.\textsuperscript{37} However, dofetilide administration was associated with a high incidence of TdP in this study.

**Drug-Device Interaction and Safety of Adjuvant Antiarrhythmic Drug Therapy**

The use of antiarrhythmic drugs to prevent ICD interventions is not without risk. Potential adverse drug-device interactions are listed in Table 1. One of the most important drug-device interactions is a drug-induced increase in defibrillation and pacing thresholds leading to failure of treatment of life-threatening arrhythmia.

This important issue was addressed in a substudy of OPTIC that measured DFTs at baseline and after 8 to 12 weeks of antiarrhythmic therapy in a subgroup of 94 patients.\textsuperscript{38} Amiodarone plus \(\beta\)-blocker therapy led to a small but statistically significant increase in DFT of 1.29 J, whereas treatment with sotalol was associated with a 0.89 J decrease. In contrast, \(\beta\)-blocker was associated with a 1.67 J decrease in DFT. It is recommended that meticulous testing of DFT be done in patients with monophasic ICDs with epicardial lead systems,\textsuperscript{39} patients with a high DFT at baseline, and those treated with high-dose,\textsuperscript{40} long-term amiodarone.\textsuperscript{41,42–44} In contrast, azimilide has been shown to have minimal effects on the DFT or pacing thresholds in ICD patients.\textsuperscript{32,45} Similarly, dronedarone has been shown to have no effects on defibrillation safety margin or pacing thresholds at its therapeutic dose or higher.\textsuperscript{36,46}

Antiarrhythmic drugs are known to increase the cycle length of VT and thus improve the hemodynamic tolerability and effectiveness of ATP in most situations. In some cases, especially with drugs such as amiodarone and sotalol, cycle length may become longer than the programmed tachycardia detection interval of the ICD, leading to failure of detection of VT.\textsuperscript{47} Appropriate adjustments in the detection algorithm are necessary when adjuvant antiarrhythmic drugs are instituted. Antiarrhythmic drugs, especially the Class IC agents, may also affect the morphology of the QRS complex and can thus interfere with morphology sensing and rhythm stability criterion, leading to incorrect rhythm interpretation by the ICD and resultant inappropriate treatment.\textsuperscript{48}
Drug-induced proarrhythmia, especially TdP, is another rare but potential problem when drugs with Class III effects such as azimilide, sotalol, dofetilide, and amiodarone are used, especially in patients with compromised repolarization reserve. Extracardiac side effects of antiarrhythmic drugs such as amiodarone are a limitation to its long-term use. This may be less of an issue with new drugs such as dronedarone and azimilide.

Catheter Ablation Therapy
Catheter-based mapping and ablation techniques have been considered a last-resort treatment for patients with recurrent VT refractory to adjuvant drug therapy. Recent clinical trials have touted catheter ablation techniques as a first-line treatment for prevention of recurrent ICD therapies including electrical storm. The efficacy of catheter-based techniques is operator-dependent and is an invasive procedure with inherent complications. Data supporting the use of catheter ablation therapy are limited and do not address issues such as quality of life and cost. We believe that antiarrhythmic drugs remain as the first-line therapy for prevention of ICD shocks for most patients.

Summary and Recommendations
Should every patient who has a defibrillator receive an antiarrhythmic drug for shock prevention? Although the data for postshock therapy is compelling, most of the studies have been carried out in patients who have received an ICD for secondary prevention of SCD. Patients who receive an ICD for primary prevention appear to have fewer device activations. Until more data are available, routine use of antiarrhythmic drugs in device patients does not appear to be warranted.

When patients need drugs because of frequent shocks, the weight of evidence supports optimizing β-blocker therapy. If they do not work or cannot be tolerated, amiodarone, azimilide, or sotalol may provide benefit. At this point, the decision as to when to start adjuvant antiarrhythmic drug therapy in patients who receive an ICD for secondary prevention should be individualized, with the expectation that well-designed therapy can reduce ICD shocks and improve quality of life. For those patients in whom well-conceived drug therapy is ineffective, ablation techniques may be useful.

Disclosures
Dr. Kowey has served as a consultant to Procter and Gamble, Berlex, Wyeth, and Sanofi-Aventis.

References


Key Words: implantable cardioverter-defibrillator • ventricular arrhythmia • antiarrhythmic drug therapy • adjuvant therapy • ICD shocks
As discussed by Patel et al, the majority of implantable cardioverter-defibrillator (ICD) patients take antiarrhythmic drugs in the hope of decreasing appropriate and inappropriate ICD shocks, in part by slowing ventricular tachycardia to make it more amenable to termination by ATP. ICD shocks are associated with an increase in mortality and a decrease in quality of life. Whether this is also true for ATP has not been conclusively determined; arrhythmias eliciting ATP may also be associated with adverse outcomes. Whether prompt medical care following an ICD intervention would improve prognosis needs to be demonstrated. Their review of antiarrhythmic drugs investigated in patients with ICDs leaves many questions unanswered. First, which drug should be started after β-blockers? Amiodarone is clearly effective but has significant side effects that frequently lead to discontinuation. Azimilide may be effective with fewer side effects (except torsade de pointes), but is not approved by the Food and Drug Administration or European authorities, and experience is limited. No comparative data for amiodarone and azimilide are available. Sotalol is less effective than amiodarone and can cause torsade de pointes. Second, when should an antiarrhythmic drug be started? Prophylactically? After one ICD shock? After multiple shocks? Early prophylactic use as in the OPTIC trial may overtreat a large group of patients who will never have an ICD intervention but are exposed to drug side effects; or the drug may elicit an ICD intervention due to proarrhythmia. Third, drugs may have limited benefit for patients with incessant ventricular tachycardia or electrical storm. In these patients, intravenous amiodarone can be effective but takes time (hours) to work, and the IV Amiodarone Multicenter Investigators Group found that survival is limited to ~60% after 30 days. Recurrent VF triggered by ventricular premature beats in patients with structurally normal hearts, ion channelopathies, or acute or subacute myocardial infarction is almost always refractory to medical treatment but can be treated with a very high success rates in experienced centers by catheter ablation. Early catheter ablation should be advocated in these situations. It can be life saving.
Should Catheter Ablation be the Preferred Therapy for Reducing ICD Shocks?

Ventricular Tachycardia in Patients With an Implantable Defibrillator Warrants Catheter Ablation

Karl-Heinz Kuck, MD

Ventricular tachycardia is the major cause (70% to 80%) of sudden cardiac death (SCD).¹ Estimates for SCD in the United States range from less than 200 000 to more than 450 000 SCDs annually.² Overall, event rates in Europe are similar to those in the United States, with significant geographic variations.³ The overall incidence of SCD in the United States is 1 to 2 per 1000 people (0.1% to 0.2%) annually. The temporal definition of SCD strongly influences epidemiological data. The proportion of all deaths due to SCD is 13% when a definition of 1 hour from onset of symptoms is used and 18.5% when a definition of 24 hours is used, as in the community-wide study in Maastricht.⁴ Almost 80% of all SCDs occur at home.⁴ The survival rate at 10% to 25% is low and has not been improved by the automatic external defibrillator (AED) in patients with moderate risk.⁵ In 80% of all SCDs coronary artery disease is the underlying heart disease.⁶

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Implantable cardioverter-defibrillators (ICDs) reduce SCD and thereby total mortality compared with antiarrhythmic drugs in high-risk patients.⁷⁻¹¹ However, patients with ICD shocks have a decreased quality of life¹² if ≥5 shocks per year are delivered¹³ and an increased mortality rate compared with patients without shocks, even if the shocks are inappropriate.¹⁴ Despite the fact that ICDs offer antitachycardia pacing therapy that may terminate some episodes of ventricular arrhythmias without the need for a shock and enhanced discrimination algorithms that may reduce the risk of inappropriate shocks,¹⁵,¹⁶ both appropriate and inappropriate ICD shocks continue to present a problem. In addition, ICD therapy does not eliminate SCD completely. A pooled analysis of all randomized ICD trials indicates a rate of ICD-unresponsive SCD of 5% and a sudden cardiac to cardiac death rate of ≈30%.¹⁷ Most of these patients die because of electromechanical dissociation after ICD shocks or because of ventricular arrhythmias after failure of the ICD to terminate ventricular tachycardia/ventricular fibrillation (VT/VF).¹⁸ Therefore, strategies beyond device programming to reduce or even to prevent ICD shocks and to reduce the rate of ICD-unresponsive SCD are urgently needed.

Two strategies, antiarrhythmic drug therapy and catheter ablation, have the potential, alone or in combination, to reduce or even prevent VT recurrences and thereby ICD shocks.

Antiarrhythmic Drugs in ICD Patients

The largest prospective, randomized trial evaluating several drug regimen in patients with an ICD for secondary prevention showed that the combination of β-blockers and amiodarone had the greatest effect, with a reduction of ICD shocks by 73% compared with the control group (β-blocker alone) and of 57% compared with the sotalol group, with an incidence of ICD shocks in the control group of approxi-
Catheter Ablation in ICD Patients

Catheter ablation of ventricular arrhythmias in patients with underlying heart disease was introduced in the early 1980s, first using direct-current energy and later, radiofrequency current (RFC). The initial acute success rates with RFC were on average 75%, with a recurrence rate of 21% over a follow-up time average of 21 months. The limitation of catheter ablation at this time was 2-fold. First, only conventional RFC (nonirrigated) was available, and second, only patients with hemodynamically tolerated, stable VT could be treated, for which an ECG of the spontaneous VT had been obtained and mapping could be performed during VT. The introduction of the electroanatomic mapping system allowed creation of ventricular geometry and displayed low-voltage areas of scar or infarction. Mapping during stable sinus or paced rhythm to identify targets for VT, the so-called substrate mapping, allows performing catheter ablation in patients with unstable, hemodynamically nontolerated VT, in patients with multiple VTs, or in patients without inducible VT. Today, most patients with recurrent VT have an ICD that promptly terminates VT, so its hemodynamic impact and ECG morphology are often unknown. Thus substrate mapping is often the only method to perform catheter ablation in patients with an ICD.

Two single-center studies have shown that catheter ablation of VT can effectively reduce the number of VT recurrences and thereby ICD interventions when 3D mapping systems are used. Such a reduction of ICD interventions is the most important objective of catheter ablation.

Catheter Ablation After Multiple ICD Interventions

In most studies, catheter ablation has been performed in patients with ischemic heart disease after multiple ICD interventions, including patients with incessant VT. In almost all of these studies, patients were included after failure of 1 or multiple antiarrhythmic drugs. The 2 largest prospective multicenter trials conducted in the United States using irrigated RFC included more than 350 patients with structural heart disease, predominantly coronary artery disease. Both studies differ with respect to patient inclusion but also to electrophysiological end points. In the cooled RFC trial, only patients with a hemodynamically stable VT were included, whereas in the thermocool trial patients with multiple VTs, unmappable VTs, and a history of prior failed VT ablation were included. In the cooled RFC trial, the acute success rate was 71% when the end point was elimination of all mappable VTs and 41% when the end point was elimination of VT of any type. In the thermocool trial, the acute success rate was 49% when elimination of all inducible VT was used as the end point. The Kaplan–Meier recurrence rate of sustained ventricular arrhythmia was 56% during 1 year of follow-up. The thermocool trial limited the follow-up time to 6 months for the efficacy end point. Freedom from VT was 53%.

In the thermocool trial, the impact of ablation on VT frequency for the 6 months before ablation and after ablation for the 142 patients (excluding those with incessant VT) who had an ICD before ablation and who completed 6 months of follow-up was considerable. VT was reduced from a median of 11.5 episodes to a median of 0 episodes per 6 months. The frequency of VT was reduced by ≥75% in 67% of patients. An increase in the number of VT episodes was observed in 20% of patients. Patients with VT recurrences were older; had more heart failure, more atrial fibrillation, multiple myocardial infarction locations, and more inducible VTs; received more radiofrequency lesions; and more often had a VT inducible after ablation compared with patients without VT recurrences.

In the cooled RFC study, a ≥75% reduction in the VT frequency in the two months after ablation compared to the two months before ablation was observed in 99 of 122 patients (81%), of whom 115 had an ICD. Only the absence of an inducible VT identified as the clinical VT was a predictor of clinical success.

The Euro-VT Study performed catheter ablation using external irrigation in 63 patients with recurrent scar-related ventricular tachycardia at 8 centers in Europe. Forty-two patients (66.7%) had an ICD before ablation, and another 9 patients (14.3%) received an ICD thereafter. The acute success rate, defined as VT termination and noninducibility...
of all clinically relevant VTs, was 81%. Clinically relevant VTs were defined as sustained VTs with equal or longer cycle lengths (CL) compared with the clinical VTs. During a follow-up of 12 months, VT recurred in 49% of patients. In patients with VT recurrences, 79% had a significant reduction of ICD therapies (antitachycardia pacing and shocks). The mean number of ICD therapies was decreased significantly from 60±70 before ablation to 14±15 (23%) in the same period of time (6 months) after ablation. The electrophysiological findings did not predict VT recurrences.

One limitation of catheter ablation studies in ICD patients must be addressed. In almost all studies, antiarrhythmic drugs were not systematically withdrawn after ablation. In the thermocool trial, antiarrhythmic drugs were continued after ablation, without change in 55% of patients, reduced in 26% of patients, and increased in 19% of patients. At last follow-up, only 28% of patients were no longer taking antiarrhythmic drug therapy (other than β-adrenergic blockers). Antiarrhythmic drug therapy was reduced more often in patients with a successful outcome; 35% of them were not taking antiarrhythmic drugs at 6 months of follow-up. In the cooled tip trial, antiarrhythmic drug therapy at the time of hospital discharge consisted of amiodarone in 42% of patients, sotalol in 12%, and a type 1 antiarrhythmic drug in 12% of patients. Although it was recommended that patients continue on the antiarrhythmic drugs they received before catheter ablation, at the time of the last follow-up, the use of these 3 drugs had decreased to 30%, 5%, and 10%, respectively. In the Euro-VT trial, antiarrhythmic drug treatment with amiodarone was present in 31 (49%) patients before ablation and stopped in 11 (17%), but initiated in 21 (33%) after ablation. Thus, a total of 41 (65%) patients received amiodarone after ablation. In 29 of them (71%), amiodarone was stopped during the first 6 months of follow-up. Therefore, any beneficial effect of catheter ablation in these studies may be influenced by drug therapy, even when most patients were drug failures before VT ablation.

Furthermore, the efficiency of catheter ablation in ICD patients must be balanced with the safety profile of this interventional procedure. In the 2 US multicenter trials, procedure-related death was 2.7%44 and 3%,45 respectively. The periprocedural mortality in the latter study was due to intractable ventricular arrhythmias in 6 of 7 patients. The 1-year actuarial mortality rate was 18% in both trials. Of the 40 deaths during follow-up in the thermocool trial, 37.5% were attributed to ventricular arrhythmias (9 patients in hospital and 5 out of hospital), and 35% were attributed to heart failure. Of the 22 non–procedure-related deaths in the cooled RFC trial, 2 were due to noncardiac causes, 16 were classified as cardiac nonarrhythmic, and 4 were presumed to be due to a ventricular arrhythmia. In the EURO-VT trial, there was no procedure-related mortality; 1 patient had prolonged cardiac arrest and died of progressive heart failure 2 months later. After an average follow-up of 12 months, mortality rate was 8%. One patient died in intractable, incessant VT 6 months after the initial procedure, 2 patients died of progressive heart failure, 1 patient died shortly after cardiac transplantation, and 1 patient died of cancer 5 months after ablation. Major complications including stroke/transient ischemic attack, complete atroventricular (AV) block, tamponade, valve injury, myocardial infarction, and so forth occurred in the 2 US trials in 8% and 10% of patients, respectively. In the Euro-VT trial, only 1 major complication (1.6%) occurred with prolonged resuscitation due to cardiac arrest.

Data on catheter ablation in ICD patients with nonischemic VT from large multicenter trials are lacking. Also, very little information from single-center studies is available on the effect of catheter ablation on ICD interventions. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) trial, the annual rate of ICD shocks was 5.1%, with a lower event rate of ICD therapy over 5 years in patients with dilated cardiomyopathy (DCM) compared with patients with ischemic heart disease.47 Also, patients with arrhythmogenic right ventricular dysplasia (ARVD) have high rates of appropriate ICD therapies over time.48 Appropriate ICD interventions occur in 78% of patients over 3.5 years. Mapping studies in patients with dilated cardiomyopathy as well as right ventricular disease have shown that reentry is the dominant mechanism in these patients. In DCM, the substrate is frequently located in the left ventricle near the ventricular base in the perivalvular region,49 whereas in ARVD, critical isthmuses for reentry are often located along the tricuspid valve annulus and/or the pulmonary annulus and the anterior/inferior walls. Ablation is often successful when a linear lesion is applied from the annulus toward a region of scar.50,51 Of note, in DCM and ARVD, more extensive scar is often present in the epicardium and not in the endocardium, compared with the majority of patients with a previous myocardial infarct.52–54 In both groups, epicardial ablation has been successfully applied after failure of endocardial ablation.52 In general, acute success rates of catheter ablation are similar as in ischemic VT patients, but recurrence rates seem to be higher.55,56 In a single-center study of 28 patients with DCM, which gives some information on the impact of catheter ablation on ICD interventions, catheter ablation eliminated all reentrant VTs in 12 of 22 patients and modified inducible VT in 4. In 6 of the 7 patients who underwent epicardial ablation after failure of endocardial ablation the VT could be abolished. During a follow-up of 334 days, 54% of all patients with myocardial reentry were free of VT. Twenty patients had an ICD before and another 6 received an ICD after ablation. For the total 28 patients, the number of VT episodes per month decreased markedly after radiofrequency ablation.52

In a single-center study of 22 patients with ARVD, catheter ablation eliminated inducible VT in 82% of patients with VT recurrences in 23% after 1 year.55 Eighteen patients (82%) had an ICD before and the remaining 4 patients received an ICD after ablation. The major indication for ablation was frequent ICD therapies in 15 patients, with a mean of 5
shocks within 30 days before ablation. No detailed information is given on the mean number of shocks after ablation. Appropriate ICD therapies for VT accounted for all 8 VT recurrences. In this study, all patients continued their antiarhythmic therapy after ablation, which mainly was amiodarone or sotalol. In a more recent single-center study in patients with ARVD, only 5 (21%) of 24 patients had an ICD at the time of catheter ablation. Over a mean follow-up time of 36 months, another 14 (58%) received an ICD. The reason for this was the rather limited long-term success rate of catheter ablation with a VT recurrence rate after a single procedure of 64% after 1 year. However, it should be mentioned that in the majority of patients the ablation procedure was not performed with a 3D mapping system, only standard RFC was delivered, and no epicardial mapping and ablation was performed.

Serious complications in these small series are infrequent, but the risks following epicardial puncture such as inadvertent puncture of the right ventricle with subsequent pericardial tamponade and, rarely, bleeding from the liver, should not be underestimated.

Catheter Ablation in ICD Patients With Incessant VT
Incessant VT is a life-threatening situation associated with high morbidity and mortality. Slow incessant VT is either not detected by the ICD, because the VT-CL is above the programmed cut-off CL of the ICD or causes multiple ICD interventions, including ICD shocks, if the VT-CL is below the programmed cut-off CL of the ICD. Even if the ICD terminates VT, VT is often reinitiated by one of the next sinus beats due to slow conduction. Catheter ablation is the only treatment option, because patients are either under antiarhythmic treatment, or, if not, antiarhythmic drugs may worsen the clinical situation due to further slowing of conduction without VT termination and due to their negative inotropic effects. In the thermocool trial, incessant VT was present in 37 of 231 patients (16%) before ablation. During follow-up, 9 (24%) had recurrence of incessant VT (4 died, and VT became controllable after repeat ablation in 3 patients and with drug therapy in 2 patients). Of the 28 patients free of incessant VT, 9 had recurrence of intermittent VT that was now terminated by the ICD. Interestingly and most importantly, in the multivariable analysis, incessant VT was associated with better outcomes. Ablation strategies from within the epicardial space may be considered as an important option in patients with incessant VT when endocardial ablation fails or cannot be attempted.

Catheter Ablation in ICD Patients With Electrical Storm
Electrical storm, characterized by very frequent arrhythmic episodes resulting in appropriate ICD shocks, is a frightening event associated with poor short- and long-term prognosis. The cardiac death rate ranges from 27% to 54% over 2 years.

Catheter ablation has been shown to abolish electrical storm in patients with and without underlying heart disease by either eliminating the trigger for VT/VF, namely ventricular premature beats, or by modifying the substrate for VT/VF. Catheter ablation significantly reduces the number of ICD interventions in patients with electrical storm. In a recent single-center study, 95 patients with electrical storm, leading to a mean number of 14 ICD shocks per patient and per day, underwent catheter ablation. Seventy-two patients had underlying coronary artery disease, 10 patients had dilated cardiomyopathy, and 13 patients had right ventricular disease. After catheter ablation, electrical storm was acutely suppressed in all patients and did not recur during follow-up of 22 months in patients in whom either no VT could be induced or the clinical VT became noninducible. Furthermore, death from any cause could significantly be reduced in both groups compared with patients in whom the clinical VT remained inducible and electrical storm recurred. Both cardiac death as well as sudden cardiac death was significantly higher in patients with electrical storm recurrences (50% versus 0%). This observation indicates that a successful VT ablation procedure may be associated with a reduction of total mortality in subgroups of patients.

Catheter Ablation of VT/VF Before ICD Interventions
Because catheter ablation significantly reduces ICD shocks in patients after multiple ICD interventions/shocks and ICD shocks are associated with increased mortality compared with patients without shocks, the true benefit of catheter ablation may be demonstrated only if ICD shocks are either completely—or at least partially prevented. Recently, 2 trials addressed the impact of early catheter ablation—before ICD shocks—in 2 different patient populations.

The SMASH-VT trial performed catheter ablation either in patients with unstable VT, VF or syncope with inducible VT before any ICD shock, or in patients with a primary ICD indication after the first ICD shock. Catheter ablation led to a 73% reduction of ICD shocks as compared with the ICD only group over a follow-up time of almost 2 years. Interestingly, a trend to fewer deaths during follow-up was seen in the ablation group. Whether this observation indicates that fewer ICD interventions after preventive catheter ablation may lead to improved survival is a challenging hypothesis.

The VTACH trial showed that catheter ablation performed before ICD implantation in patients after the first episode of a hemodynamically stable VT significantly prolonged the median time to first VT/VF from 5.9 months to 18.6 months. The benefit was more pronounced in patients with left ventricular ejection fraction >30%. Furthermore, catheter ablation reduced the overall incidence of appropriate ICD interventions by 28% and the incidence of ICD shocks by 43%. Even more importantly, catheter ablation reduced the
median number of appropriate ICD interventions per patient and year of follow-up by 93%. In addition, catheter ablation significantly reduced the rate of hospitalizations for cardiac reasons.72

The complication rate becomes even more important if an interventional procedure is performed prophylactically. In both trials, the incidence of ablation related death was 0% and of major complications 4.7%71 and 3.8%,72 respectively.

**Final Considerations**

Catheter ablation reduces VT/VF recurrences and thereby ICD interventions including ICD shocks by ≈75% in patients after multiple ICD shocks. In this patient population, the incidence of procedure-related death ranges from 0% to 3%, and the incidence of major complications from 3.6% to 10%. More importantly, catheter ablation is the only treatment to terminate and eliminate incessant VT and to acutely abolish electrical storm in ICD patients. In the latter group of patients, it improves prognosis if ablation is successful. Catheter ablation also reduces VT/VF recurrences and thereby ICD shocks by 43% to 73% when applied prophylactically, that is, before any ICD shock has been delivered. Interestingly, in this patient population the ablation-related mortality rate was 0%, and major complications occurred in 3.8% to 4.7%. Whether the lower incidence of procedure-related mortality and major complications favors an early (prophylactic) ablation procedure compared with a late procedure (after multiple shocks) requires further investigation. In clinical practice, many ICD patients are referred very late for catheter ablation and therefore have the negative consequences of ICD shocks, which may also lead to a higher mortality and complication rates. Catheter ablation should be performed immediately in patients with electrical storm and incessant VT. Catheter ablation should be strongly considered prophylactically in patients with left ventricular ejection fraction <35% and ischemic heart failure New York Heart Association class III, in whom 1 or more ICD shocks are associated with 1-year mortality rates of 64% and 62%, respectively.14 Furthermore, catheter ablation should be performed in patients with low left ventricular ejection fraction at ≥2 appropriate ICD shocks, because the risk of death is increased by factor 8.14 Of course, individual patient factors must be considered.

Several issues remain unclear and require further research. First, in all studies, patients underwent catheter ablation either after multiple ICD interventions or before any ICD intervention. Therefore, the question on the optimal time of catheter ablation in ICD patients remains unanswered until a randomized trial has been performed. Second, except for SMASH-VT, no study has consequently stopped antiarrhythmic drug treatment after catheter ablation. Therefore, any beneficial effect can be a combination of both drug and ablation therapy, even when most patients were drug failures before catheter ablation was successfully performed. In clinical practice, catheter ablation is often used as an adjunct to antiarrhythmic drug therapy or vice versa. Third, no study has been performed to randomize catheter ablation versus antiarrhythmic drug therapy. Therefore, no final comment can be made on the relative efficacy of these two therapeutic strategies.

Fourth, hemodynamically stable patients with VT with underlying heart disease and reduced left ventricular function undergo generally ICD treatment without proof of benefit by a randomized ICD trial. It is also currently unclear and unproven whether catheter ablation in this patient population can replace the ICD. This is also true for other patient populations with underlying heart disease. It would require a currently unproven positive impact of catheter ablation on sudden cardiac death. Fifth, no study has been powered to test whether prevention—or a significant reduction of ICD interventions/shocks by catheter ablation—leads to a reduction of total mortality. Sixth, various ablation techniques, acute end points for ablation, ICD programming, and follow-up times have been used in studies. All of those parameters influence the acute and chronic results. Therefore, urgent standardization with a requirement on minimal data reporting is mandatory to make the results of future studies better comparable. This perception has led to a recent consensus paper on catheter ablation of ventricular arrhythmias by EHRA and HRS.73

Finally, catheter ablation of VT/VF must become easier, particularly epicardial ablation, and even more effective. Above all, the long-term results must be improved.

It should be kept in mind that most catheter ablation studies have a rather short follow-up. Follow-up, in part, may be negatively influenced by the progress of the underlying heart disease. Therefore, it is unclear whether early or even prophylactic catheter ablation will prevent “late” VT/VF and SCD. Nevertheless, better mapping tools and new energy sources or a better understanding on how to make better lesions using “old” energy sources such as irrigated radiofrequency by implementing real-time contact force measurements, and so forth, are necessary to improve the acceptance of catheter ablation of VT/VF and to attract more physicians to get involved with a treatment strategy which has revolutionized the treatment of arrhythmias over the last decades and did help so many patients. Catheter ablation has become the treatment of choice for almost all supraventricular arrhythmias. Catheter ablation has become a valuable treatment option for atrial fibrillation. Catheter ablation has become the first-line treatment for idiopathic VT. Catheter ablation will become the treatment of choice for VT with underlying heart disease, not only in ICD patients—it may even challenge the ICD one day in some patient populations. Then the debate is over. The best prevention of ICD shocks is the prevention of the ICD.

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The erudite article by Kuck provides a complete review of catheter ablation for ventricular tachycardia (VT) and fibrillation that result in implantable cardioverter-defibrillator (ICD) shocks. We agree that there are no data regarding the comparative efficacy of antiarrhythmic drugs versus catheter ablation for treatment of ICD shocks. A wide diversity of end points and study conditions make interpretation of current data difficult. As Kuck states, catheter ablation has been used as an effective adjunct therapy for treatment of recurrent VT, but we don’t know if ablation saves life, and more importantly, the best time to use catheter ablation is unclear. We believe there is no fundamental disagreement; until we know more about ablation, drugs will continue to be the first-line therapy for prevention and treatment of ICD shocks. As we described in our article, multiple clinical trials have shown that antiarrhythmic drugs are highly effective in a wide array of patients, and they are safe to use when carefully monitored. We were surprised that Kuck didn’t refer to SHIELD, a landmark trial that demonstrated the efficacy and safety of azimilide. This study is important for its precise methodology and clear conclusions. We further agree that catheter ablation is the treatment of choice for patients who have failed multiple antiarrhythmic drugs and have incessant VT or electrical storm, stressing that the majority of these patients still need antiarrhythmic drugs after ablation to prevent recurrent VT. The important question that remains is should ablation be used instead of drugs or even prophylactically? Given the complexity of the procedure and attendant complications, and given that the success of catheter ablation is highly operator dependent, the outcomes obtained in the SMASH-VT trial cannot be extrapolated to the world of clinical practice. Furthermore, catheter ablation will likely never be first-line therapy for primary prevention patients whose risk of ICD shocks is low, for patients who have multiple potential substrates for VT, for patients with inherited channelopathies such as long-QT, short-QT or J-wave syndromes, or for patients who have other triggering arrhythmias such atrial fibrillation that can not be ablated. So for now and in the foreseeable future, antiarrhythmic drugs are first-line therapy for prevention and treatment of ICD shocks, with catheter ablation positioned to be used when drugs fail.
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