Implantable Cardioverter-Defibrillator Therapy for Prevention of Sudden Death in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

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Background—Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a condition associated with the risk of sudden death (SD).

Methods and Results—We conducted a multicenter study of the impact of the implantable cardioverter-defibrillator (ICD) for prevention of SD in 132 patients (93 males and 39 females, age 40±15 years) with ARVC/D. Implant indications were a history of cardiac arrest in 13 patients (10%), sustained ventricular tachycardia in 82 (62%), syncope in 21 (16%), and other in 16 (12%). During a mean follow-up of 39±25 months, 64 patients (48%) had appropriate ICD interventions, 21 (16%) had inappropriate interventions, and 19 (14%) had ICD-related complications. Fifty-three (83%) of the 64 patients with appropriate interventions received antiarrhythmic drug therapy at the time of first ICD discharge. Programmed ventricular stimulation was of limited value in identifying patients at risk of tachyarrhythmias during the follow-up (positive predictive value 49%, negative predictive value 54%). Four patients (3%) died, and 32 (24%) experienced ventricular fibrillation/flutter that in all likelihood would have been fatal in the absence of the device. At 36 months, the actual patient survival rate was 96% compared with the ventricular fibrillation/flutter-free survival rate of 72% (P<0.001). Patients who received implants because of ventricular tachycardia without hemodynamic compromise had a significantly lower incidence of ventricular fibrillation/flutter (log rank=0.01). History of cardiac arrest or ventricular tachycardia with hemodynamic compromise, younger age, and left ventricular involvement were independent predictors of ventricular fibrillation/flutter.

Conclusions—In patients with ARVC/D, ICD therapy provided life-saving protection by effectively terminating life-threatening ventricular arrhythmias. Patients who were prone to ventricular fibrillation/flutter could be identified on the basis of clinical presentation, irrespective of programmed ventricular stimulation outcome. (Circulation. 2003;108:3084-3091.)

Key Words: cardiomyopathy ■ death, sudden ■ defibrillation ■ prevention ■ tachyarrhythmias

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a heart muscle disease, often familial, characterized by fibrofatty replacement of the right ventricular myocardium that underlies ventricular arrhythmias.1–5 The natural history of the disease is related to either sudden arrhythmic death in young people or heart failure that occurs predominantly later in life.3–7 Although this disease has become an emerging indication for implantable cardioverter-defibrillators (ICDs) in the setting of cardiomyopathies for prevention of sudden death (SD),8 there are few published data on the efficacy and safety of this therapy.9–11 Because identification of clinical findings that predict outcome has been elusive, there is a growing tendency to implant an ICD once the disease has been diagnosed, regardless of risk stratification.12 Furthermore, major concerns have been raised about the risk of perforation due to lead implantation into the right ventricle and about the difficulty in maintaining adequate sensing and pacing thresholds during follow-up be-
cause of the progressive loss of right ventricular myocardium. We conducted an observational, multicenter study to determine the impact of ICD therapy, exclusively based on electrograms stored by the device, for prevention of SD in a large patient population with ARVC/D.

Methods

Participating Centers

Patients were recruited at 22 institutions in north Italy (114 patients, 59 of whom were from the Veneto Region) and at 1 institution in the United States (18 patients; see Appendix). All major electrophysiology centers from north Italy with experience in the use of implantable ICDs in patients with ARVC/D were invited to participate in the study. The US center was involved because of its previously reported largest experience in North America of ICD therapy in ARVC/D.10

Enrollment Criteria

The 132 patients enrolled in the study were consecutive patients at each institution who met the enrollment criteria. Patients had to have an unequivocal diagnosis of ARVC/D. All patients fulfilled either 2 major or 1 major plus 2 minor diagnostic criteria recommended by the Task Force of the European Society of Cardiology.13 To enhance the specificity of diagnosis, no patient with only minor criteria entered the study. Special attention was paid to exclude idiopathic right ventricular outflow tract tachycardia, myocarditis, idiopathic dilated cardiomyopathy, and Uhl anomaly. Patients also had to have successful implantation of an ICD that provided stored intracardiac electrograms, and a follow-up period of at least 6 months after implantation of the ICD was required.

ICDs and Stored Intracardiac Electrograms

The ICDs were implanted between January 1992 and December 2001; 112 (85%) of 132 patients underwent implantation after January 1, 1995. Implantation was performed through a thoracotomy with epicardial lead systems in 4 patients (3%) or transvenously in 128 (97%). In all patients, the threshold for converting ventricular fibrillation was tested at the time of implantation, and every effort was made to achieve defibrillation with a 10-J safety margin. All ICDs provided either single-chamber (98 patients, 74%) or dual-chamber (34 patients, 26%) antibradycardia pacing. All devices had diagnostic memory and were capable of recording and storing intracardiac electrograms, for prevention of SD in a survivor until transplant, at which time they were censored from continued analysis.

Survival Projection

To evaluate the potential impact of the ICD on survival, projected mortality curves (ie, SD-free survival rates in the absence of ICD therapy) were estimated, with the first appropriate ICD intervention on ventricular fibrillation/flutter as the defined end point. This analysis of projected survival was restricted to episodes of ventricular fibrillation/flutter that show no tendency to be self-terminating and usually result in SD unless corrective measures are undertaken promptly.14

Characteristics of the Patients

The study population consisted of 132 patients, aged 15 to 72 years (mean 40±15 years; Table 1). Seventy patients (53%) were <40 years old, and 93 patients (70%) were male. At the time of implantation, 127 of the 132 patients had no or mild functional limitation, and 5 had severe symptoms.

Right and left ventricular function were evaluated by both angiography (118 patients; 89%) and echocardiography (all patients). Left ventricular involvement was diagnosed in the presence of an angiographic ejection fraction <55%. At angiography, right ventricular ejection fraction ranged from 15% to 68% (mean 47±11%), and left ventricular ejection fraction ranged from 28% to 71% (mean 55±9%). In patients with isolated right ventricular involvement, the mean value of left ventricular ejection fraction was 64±3% at angiography and 61±6% at echocardiography. Antiarrhythmic drug therapy before ICD implantation was prescribed in 110 (83%) of 132 patients and consisted of sotalol in 43 (39%), amiodarone (either alone in 19 [17%] or in combination with β-blockers in 26 [24%]), β-blockers in 13 (12%), and flecainide in 9 (8%).

Electrophysiological study before ICD implantation was performed in 111 (84%) of 132 patients. All antiarrhythmic drugs were discontinued ≥5 half-lives (>6 weeks for amiodarone) before the study. Programmed ventricular stimulation was performed according to each institution’s protocol; however, in all cases, a minimum of 2 drive-cycle lengths and up to 3 ventricular extrastimuli were used while pacing from 2 right ventricular sites. The stimulation protocol was repeated after intravenous isoprenaline infusion in 26 patients (23%). Programmed ventricular stimulation was considered positive if a sustained ventricular tachyarrhythmia, ie, one that lasted >30 seconds or required termination because of hemodynamic compromise, was induced. Ninety-eight patients (88%) were inducible to either sustained ventricular tachycardia (67 patients; 68%), with a mean cycle length of 284±66 ms (range 210 to 415 ms), or ventricular fibrillation (31 patients; 32%).

Statistical Analysis

Results are expressed as range and mean±SD. Categorical differences between groups were evaluated by Fisher’s exact text or χ². Differences between group means were compared by unpaired t test. The independent correlation of clinical variables (age; gender; family history of sudden death; nonsustained ventricular tachycardia; history of cardiac arrest or ventricular tachycardia with and without hemodynamic compromise; syncope; right ventricular ejection fraction; left ventricular ejection fraction; therapy with any antiarrhythmic drugs, sotalol, or amiodarone [alone or in combination with β-blockers]; and induction of ventricular tachycardia or ventricular fibrillation at programmed ventricular stimulation) with the occurrence of ventricular fibrillation/flutter was determined by means of multivariate logistic regression analysis. All variables with a probability value <0.1 in the univariate analysis were considered for entry into the multivariable model. Event-free survival rates were estimated by the Kaplan-Meier method and compared by log rank. Patients referred for orthotopic heart transplantation were included among survivors until transplant, at which time they were censored from continued analysis.

All probability values reported are 2-sided, and a probability value <0.05 was considered to be statistically significant. SAS software (SAS Institute) was used for statistical analysis.
Results

Implant Indications
The predominant clinical reasons for ICD implantation were a history of cardiac arrest in 13 patients (10%); sustained ventricular tachycardia with hemodynamic compromise in 52 (39%), ie, which caused syncope in 39 and hemodynamic collapse in 13 patients; sustained ventricular tachycardia without hemodynamic compromise in 30 (23%); unexplained syncope in 21 (16%); nonsustained ventricular tachycardia (ie, 3 consecutive premature ventricular beats, with a rate ≥100 bpm, lasting <30 seconds) on either Holter monitoring or exercise stress testing in 12 (9%); and a family history of 1 or more premature (<35 years old) SDs due to ARVC/D in 4 (3%).

Follow-Up
During a mean follow-up of 39±27 months (3.3 years), there were 4 deaths (3%; Table 1). One death was due to a storm of recurrent episodes of ventricular flutter that triggered multiple appropriate ICD discharges and finally resulted in refractory ventricular fibrillation, 1 was due to progressive congestive heart failure, 1 was due to acute endocarditis resulting from a pocket infection, and 1 was due to sudden cardiac arrest after device explantation because of pocket infection. In addition, 3 patients underwent orthotopic heart transplantation because of either biventricular heart failure (2 patients) or intractable ventricular fibrillation (1 patient). Patients who died had experienced 1 to 8 appropriate ICD interventions.

Appropriate Interventions
Sixty-four (48%) of 132 patients received a total of 1271 appropriate ICD interventions for episodes of ventricular tachyarrhythmias. Ten had a single intervention, 25 had 2 to 5 interventions, and 29 had >5 interventions, including 5 patients with ventricular tachycardia storm (3 or more clusters of multiple, consecutive appropriate discharges within 24

<table>
<thead>
<tr>
<th>Events</th>
<th>All Patients (n=132)</th>
<th>Cardiac Arrest (n=13)</th>
<th>VT With Hemodynamic Compromise (n=52)</th>
<th>VT Without Hemodynamic Compromise (n=30)</th>
<th>Unexplained Syncope (n=21)</th>
<th>Other* (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4 (3)</td>
<td>3 (23)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>SD</td>
<td>2 (1)</td>
<td>1 (8)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (1)</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1 (1)</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Heart transplantation</td>
<td>3 (2)</td>
<td>1 (8)</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2 (2)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Refractory ventricular fibrillation</td>
<td>1 (1)</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Appropriate interventions</td>
<td>64 (48)</td>
<td>9 (69)</td>
<td>28 (54)</td>
<td>14 (47)</td>
<td>8 (38)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Triggered by ventricular fibrillation/flutter</td>
<td>32 (24)</td>
<td>8 (62)</td>
<td>15 (29)</td>
<td>1 (3)</td>
<td>5 (24)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Triggered by sustained VT</td>
<td>32 (24)</td>
<td>1 (8)</td>
<td>13 (25)</td>
<td>13 (43)</td>
<td>3 (14)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>≥2 Interventions triggered by ventricular fibrillation/flutter</td>
<td>23 (17)</td>
<td>6 (46)</td>
<td>10 (19)</td>
<td>1 (3)</td>
<td>4 (19)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Inappropriate interventions</td>
<td>21 (16)</td>
<td>3 (23)</td>
<td>9 (17)</td>
<td>6 (20)</td>
<td>1 (5)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Atrial fibrillation or supraventricular tachycardia</td>
<td>10 (8)</td>
<td>1 (8)</td>
<td>5 (10)</td>
<td>3 (10)</td>
<td>1 (5)</td>
<td>0</td>
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<tr>
<td>Sinus tachycardia</td>
<td>9 (7)</td>
<td>1 (8)</td>
<td>4 (8)</td>
<td>3 (10)</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Oversensing</td>
<td>2 (2)</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Antiarrhythmic drugs at first appropriate intervention</td>
<td>53/64 (83)</td>
<td>7/8 (78)</td>
<td>24/28 (86)</td>
<td>11/14 (79)</td>
<td>7/8 (87)</td>
<td>4/5 (80)</td>
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<tr>
<td>Amiodarone</td>
<td>5 (8)</td>
<td>2 (22)</td>
<td>3 (11)</td>
<td>1 (7)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Amiodarone plus β-blockers</td>
<td>6 (9)</td>
<td>2 (22)</td>
<td>4 (14)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>β-Blockers</td>
<td>13 (20)</td>
<td>0</td>
<td>7 (25)</td>
<td>0</td>
<td>3 (38)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Flecainide</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Sotalol</td>
<td>28 (44)</td>
<td>3 (33)</td>
<td>10 (36)</td>
<td>9 (64)</td>
<td>4 (50)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Without therapy</td>
<td>11 (17)</td>
<td>2 (22)</td>
<td>4 (14)</td>
<td>3 (21)</td>
<td>1 (12)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Nonfatal complications</td>
<td>19 (14)</td>
<td>2 (15)</td>
<td>10 (19)</td>
<td>4 (13)</td>
<td>2 (10)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Lead malfunctions (lead fracture or migration)</td>
<td>5 (4)</td>
<td>1 (8)</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>1 (5)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Undersensing</td>
<td>4 (3)</td>
<td>0</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Increased pacing threshold</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Increased defibrillation threshold</td>
<td>4 (3)</td>
<td>1 (8)</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection requiring removal of defibrillator</td>
<td>2 (2)</td>
<td>0</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding or pocket hematoma</td>
<td>3 (2)</td>
<td>0</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia. Data are n (%).
hours). The interventions were defibrillation shocks in 31 patients, antitachycardia pacing in 13, and both in 20.

The age at which the first appropriate intervention occurred ranged from 19 to 69 years (mean 40 ± 13 years). The interval between implantation of the ICD and the initial appropriate intervention ranged from 2 months to 8 years (mean, 22 ± 26 months). The interval was 4 years in 9 patients.

The rate of appropriate interventions for the overall study group was 15% per year. There was no difference between Italian and US patients (14.9% versus 15.5% per year). Appropriate ICD intervention rates were similar in patients presenting with cardiac arrest, ventricular tachycardia with or without hemodynamic compromise, or unexplained syncope (Figure 1).

Sixty-eight patients (52%) did not experience any appropriate ICD intervention; 51 (75%) of these patients received concomitant antiarrhythmic drug therapy, and 8 (14%) of the 56 who underwent programmed ventricular stimulation were not inducible. None of the asymptomatic patients who were implanted because of a family history of SD experienced appropriate ICD interventions, regardless of programmed ventricular stimulation outcome.

Survival Projection
Analysis of the stored electrograms showed that 32 (24%) of 132 patients had 1 or more episodes of either ventricular fibrillation (15 patients), ventricular flutter (13 patients), or both (4 patients) that were successfully recognized and terminated by the device. Shock therapy was preceded by symptoms of initial hemodynamic compromise in all patients (syncope in 20 patients and presyncope in 12). Interval between implantation and first ICD intervention triggered by ventricular fibrillation/flutter ranged from 2 to 97 months (mean 24 ± 26 months).

Figure 2 shows actual patient survival rates compared with projected SD-free survival rates without the ICD. Actual patient survival rates were 99% at 12 months, 98% at 24 months, and 96% at 36 months of follow-up. By comparison, ventricular fibrillation/flutter-free survival rates were 88%, 79%, and 72% (P < 0.001) at the corresponding intervals. At 36 months, the estimated survival of the general population matched for age, gender, and race was 99.5%.

Patients who had ICDs implanted because of ventricular tachycardia without hemodynamic compromise had a statistically significant lower incidence (1% per year of follow-up) of ventricular flutter/fibrillation than those implanted because of cardiac arrest or ventricular tachycardia with hemodynamic compromise (10% per year of follow-up) or unexplained syncope (8% per year of follow-up; Figure 3).

Multivariate analysis identified history of either cardiac arrest or ventricular tachycardia with hemodynamic compromise, decreasing age, and decreasing left ventricular ejection fraction as statistically significant predictors for ventricular fibrillation/flutter. Unexplained syncope reached borderline statistical significance (Table 2).

Antiarrhythmic Drugs
Fifty-three (83%) of the 64 patients with appropriate interventions received concomitant antiarrhythmic drug therapy at the time of first ICD intervention (Table 1). The incidence of ICD discharges did not differ between patients who did and did not receive antiarrhythmic drug therapy (either sotalol or any antiarrhythmic drug), regardless of clinical presentation (Table 3).

Electrophysiological Study
Of 98 patients who were inducible at programmed ventricular stimulation, 50 (51%) did not experience ICD therapy during the follow-up, whereas 7 (54%) of 13 noninducible patients had ICD interventions. Overall, the positive predictive value of programmed ventricular stimulation was 49%, the negative
predictive value was 54%, and the test accuracy was 49%. The incidence of appropriate ICD discharge did not differ between patients who were or were not inducible at programmed ventricular stimulation, regardless of clinical presentation (Table 4). The type of ventricular tachyarrhythmia inducible at the time of electrophysiological study did not predict the occurrence of ventricular fibrillation/flutter during follow-up.

Inappropriate Interventions and Complications
Twenty-one (16%) of the 132 patients had inappropriate interventions and 19 (14%) had complications, (Table 1). During follow-up, 5 patients required an additional septal lead because of undersensing (in 4) or pacing failure (in 1). Four patients needed additional patches (subcutaneous and/or epicardial) and high-energy devices to achieve ventricular fibrillation conversion within a 10-J margin at implantation. One of these patients had such a marked increase in intracardiac defibrillation threshold that it necessitated cardiac transplantation 2 years after implantation.

**Table 2. Independent Clinical Characteristics Associated With Occurrence of Appropriate ICD Interventions Triggered by Ventricular Fibrillation/Flutter**

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/5 y</td>
<td>0.007</td>
<td>0.77</td>
<td>0.57–0.96</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.037</td>
<td>0.94</td>
<td>0.89–0.95</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>&lt;0.001</td>
<td>79</td>
<td>6.8–90.6</td>
</tr>
<tr>
<td>Ventricular tachycardia with hemodynamic compromise</td>
<td>0.015</td>
<td>14</td>
<td>1.7–21.1</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>0.07</td>
<td>7.5</td>
<td>0.84–1.81</td>
</tr>
</tbody>
</table>

*OR per 5-year interval.

**Figure 3.** Kaplan-Meier curves of freedom from ICD interventions on ventricular fibrillation/flutter for different patient subgroups stratified for clinical presentation. Patients presenting with ventricular tachycardia without hemodynamic compromise had significantly lower incidence of ventricular fibrillation/flutter during follow-up.

**Discussion**
This large observational study addressed the clinical impact of ICD therapy on the natural history of patients with ARVC/D treated for prevention of SD. The major finding was that nearly half of the patients had at least 1 episode of ventricular tachyarrhythmia that required ICD intervention despite antiarrhythmic drug therapy over a mean follow-up period of 3.3 years, and 24% experienced ventricular fibrillation/flutter that in all likelihood would have been fatal without termination by the device. This high incidence of ICD interventions is in agreement with data from smaller series of patients with ARVC/D previously reported by Breithard et al9 (9 of 18 patients; 50%), Link et al10 (8 of 12 patients; 67%), and Tavernier et al11 (7 of 9 patients; 78%).

**Survival Benefit of ICD Therapy**
Analysis of the incidence of ICD interventions that were triggered by ventricular fibrillation/flutter suggests a significant improvement in survival through the follow-up period, with an actual total patient survival rate of 96% compared with a 72% ventricular fibrillation/flutter-free survival rate at 36 months.

In the present study, the mean age of patients undergoing ICD implantation was 40 years, with a wide age range from 15 to 72 years. Only 5 patients had significant functional limitations at the time of implantation, and in 2 of them, biventricular heart failure worsened during follow-up, leading to death and heart transplantation, respectively. Therefore, survival benefits offered by ICD therapy are likely to be greater in ARVC/D than in older patients with coronary artery disease in whom the concurrent ventricular dysfunction is itself a limitation in longevity.16

**Risk Predictors and Indications for ICD Implant**
The present study indicates that history of either cardiac arrest or ventricular tachycardia with hemodynamic compromise, younger age, and left ventricular involvement are independent predictors of potentially lethal ventricular arrhythmias and can help in identifying those ARVC/D patients who would benefit most from ICD implantation. In the present study, patients who received an ICD because of either cardiac arrest or ventricular tachycardia with hemodynamic compromise experienced a high incidence of ventricular fibrillation/flutter (10% per year of follow-up) despite antiarrhythmic drug therapy, thus confirming that they were ideal candidates for ICD therapy. Patients presenting with unexplained syncope derived much benefit from ICDs because of the similar annual rate of resuscitative ICD interventions (8% per year of follow-up). On the other hand, patients implanted because of ventricular tachycardia without hemodynamic compromise had a statistically significant better outcome. Only 1 patient (3%) from this category had episodes of ventricular fibrillation/flutter during follow-up. When one takes into account the side effects and complications of the ICD, it does not appear to be justified to implant an ICD in this subgroup of patients.

These findings are in agreement with those of studies in patients with ischemic heart disease that demonstrated a lower SD rate in the subgroup with hemodynamically well-
tolerated ventricular tachycardia compared with cardiac arrest survivors. In patients with ARVC/D, ventricular fibrillation has been associated with active phases of myocyte death occurring in younger affected patients with progressive disease, whereas hemodynamically well-tolerated monomorphic ventricular tachycardia is caused by a reentry mechanism around a stable myocardial scar as the result of a healing process that occurs in a later stage of the disease course. This view is reinforced by the present finding that younger age is an independent risk factor for ventricular fibrillation/flutter.

Fontaine et al reported a bimodal distribution of left ventricular ejection fraction in ARVC/D patients, with mean values of 58% and 25%, respectively, and advanced the hypothesis that this pattern was accounted for by a superimposed factor, such as acute myocarditis leading to hemodynamic deterioration of the left ventricle. The subgroup of patients with severe left ventricular dysfunction showed an increased mortality rate due to congestive heart failure. The present study extended this previous observation and showed that a biventricular cardiomyopathy/dysplasia is also a predictor of worse arrhythmic outcome. The role of an arrhyth-
mogenic cofactor in association with left ventricular involvement remains to be established.

None of the asymptomatic ARVC/D patients who underwent ICD implantation for a family history of SD experienced appropriate ICD interventions during follow-up. However, the number of asymptomatic ARVC/D patients who received an ICD because of malignant family history or nonsustained ventricular tachycardia was too small to establish the need for prophylactic ICD therapy.

The electrophysiological study was of limited value in identifying patients at risk of lethal ventricular arrhythmias. Programmed ventricular stimulation showed a low predictive accuracy, with approximately 50% of both false-positive and false-negative results. This finding is in keeping with the limited predictive value of electrophysiological study in conditions other than ischemic heart disease, such as hypertrophic and dilated cardiomyopathy.

Although precise data on the efficacy of ICDs compared with antiarrhythmic therapy cannot be derived from the present nonrandomized study, the majority of appropriate interventions occurred despite concomitant therapy with sotalol, amiodarone, or β-blockers (alone or in combination).
This finding highlights the fact that the protection provided by an ICD against life-threatening ventricular arrhythmias may be superior to these drugs.

Inappropriate Interventions and Complications

Inappropriate therapy occurred in 16% of patients in the present study compared with 33% of those reported by Link et al.10 and 44% of patients in the study by Tavernier et al. 11 This discrepancy may be explained by our greater use of β-blockers and sotalol, which reduced the number of inappropriate interventions caused by sinus tachycardia or supraventricular tachyarrhythmias. Moreover, nearly 25% of the patients in the present study had dual-chamber detection algorithms that improved discrimination of ventricular from supraventricular arrhythmias.

Complications included 1 patient death from endocarditis due to a pocket infection. During follow-up, 5 patients required an additional septal lead owing to loss of ventricular sensing/pacing functions, most likely because of progressive replacement of right ventricular myocardium by fibrofatty tissue. On the other hand, in the patient who underwent cardiac transplantation because of an exaggerated increase of intracardiac defibrillation threshold, we did not find any specific clinical or pathological heart findings that could explain this complication.

Potential Study Limitations

The study design was that of an observational survey of 23 collaborative medical centers, with possible limitations in patient selection. However, for any inheritable cardiac diseases, such as hypertrophic cardiomyopathy,15 cardiac ion channel diseases,9,21,22 and ARVC/D, a prospective, randomized study design is difficult to perform for ethical reasons and because of practical limitations predominantly linked to relatively low disease prevalence and low event rate. A further limitation for a prospective study is the long periods of latency of arrhythmic events that lasted 4 or more years in 14% of patients who experienced ICD interventions.

Conclusions

ICD therapy provides life-saving protection by effectively terminating life-threatening arrhythmias in patients with ARVC/D treated for prevention of SD. Patients who are prone to ventricular fibrillation/flutter and who are candidates for ICD implantation can be identified on the basis of clinical presentation. The low predictive value of programmed ventricular stimulation makes its application in risk stratification questionable.

Appendix

The following centers and investigators participated in the study: Università di Padova (Padova, Italy), C. Basso, B. Bauce, G. Buja, D. Corrado, L. Daliento, S. Iliceto, L. Leoni, F. Maddalena, A. Nava, A. Ramondo, and G. Thiene; New England Medical Center and Tufts University School of Medicine (Boston, Mass), M.S. Link and N.A.M. Estes III; Cliniche Gavazzeni (Bergamo, Italy), M. Zardini; Cardiologia Azienda USL (Bologna, Italy), F. Naccarella; Ospedale Civile (Bolzano, Italy), W. Rauhe; Divisione di Cardiologia, Spedali Riuniti (Brescia, Italy), A. Curnis; Ospedale P. Cosma (Camposampiero, Italy), P. Turrini and R. Verlato; Ospedale Civile (Congènago, Italy), L. Corò and P. Delise; Ospedale Civile (Legnago, Italy), I. Diran; Ospedale Umberto I (Mestre, Italy), A. Corrado, G. Gasparini, and A. Raviele; Centro Cardiologico Monzino (Milano, Italy), P. Della Bella and C. Carubucci; Istituto
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References

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