Prophylactic Implantable Defibrillator in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia and No Prior Ventricular Fibrillation or Sustained Ventricular Tachycardia

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Background—The role of implantable cardioverter-defibrillator (ICD) in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation (VF) or sustained ventricular tachycardia is an unsolved issue.

Methods and Results—We studied 106 consecutive patients (62 men and 44 women; age, 35.6±18 years) with arrhythmogenic right ventricular cardiomyopathy/dysplasia who received an ICD based on 1 or more arrhythmic risk factors such as syncope, nonsustained ventricular tachycardia, familial sudden death, and inducibility at programmed ventricular stimulation. During follow-up of 58±35 months, 25 patients (24%) had appropriate ICD interventions and 17 (16%) had shocks for life-threatening VF or ventricular flutter. At 48 months, the actual survival rate was 100% compared with the VF/ventricular flutter–free survival rate of 77% (log-rank P=0.01). Syncope significantly predicted any appropriate ICD interventions (hazard ratio, 2.94; 95% confidence interval, 1.83 to 4.67; P=0.013) and shocks for VF/ventricular flutter (hazard ratio, 3.16; 95% confidence interval, 1.39 to 5.63; P=0.005). The positive predictive value of programmed ventricular stimulation was 35% for any appropriate ICD intervention and 20% for shocks for VF/ventricular flutter, with a negative predictive value of 70% and 74%. None of the 27 asymptomatic patients with isolated familial sudden death had appropriate ICD therapy. Twenty patients (19%) had inappropriate ICD interventions, and 18 (17%) had device-related complications.

Conclusions—One fourth of patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior sustained ventricular tachycardia or VF had appropriate ICD interventions. Syncope was an important predictor of life-saving ICD intervention and is an indication for ICD. Prophylactic ICD may not be indicated in asymptomatic patients because of their low arrhythmic risk regardless of familial sudden death and programmed ventricular stimulation findings. Programmed ventricular stimulation had a low predictive accuracy for ICD therapy. (Circulation. 2010;122:1144-1152.)

Key Words: cardiomyopathy ■ death, sudden ■ electrophysiology ■ implantable cardioverter-defibrillators ■ tachyarrhythmias

The implantable cardioverter-defibrillator (ICD) is standard therapy for the prevention of sudden death (SD) in patients with arrhythmogenic right ventricular (RV) cardiomyopathy/dysplasia (ARVC/D). There is general agreement that ICD therapy is indicated in patients who survived an episode of ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) because of their high incidence of arrhythmia recurrences. However, indications for prophylactic ICD therapy in ARVC/D patients with no previous history of sustained tachyarrhythmias or cardiac arrest are...
still an unsolved issue. In these patient subgroups, the identification of clinical markers of poor prognosis has been elusive, and the value of programmed ventricular stimulation (PVS) for arrhythmia risk assessment remains to be demonstrated. Current practice frequently is to implant an ICD once ARVC/D has been diagnosed, although to date the benefit of ICD therapy according to risk stratification is unknown.

Clinical Perspective on p 1152

The present multicenter international study investigated the incidence, efficacy, and safety of ICD therapy in a large series of patients with ARVC/D who did not have prior VF or sustained VT and received a device because they were considered at risk for SD. To gain insights for arrhythmic risk stratification in this ARVC/D patient population during a long-term follow-up, we analyzed the value of clinical and electrophysiological variables for the prediction of appropriate ICD discharges on life-threatening ventricular tachyrhythmias, which were identified by the analysis of stored electrograms of implanted ICDs.

Methods

Study Population

The study population consisted of 106 patients with ARVC/D and no prior sustained VT or VF who received prophylactic implantation of ICDs for prevention of SD. Patients were recruited at 6 collaborative medical centers in Europe and the United States and were consecutive patients at each institution.

All patients fulfilled diagnostic criteria for ARVC/D recommended by the task force of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Detailed diagnostic evaluation included basal 12-lead ECG, exercise testing, 24-hour Holter monitoring, 2-dimensional echocardiography, left and right ventriculography, and coronary angiography. The clinical decisions relative to risk status and ICD implantation were made at each participating center according to customary practice by the local electrophysiologist and using recognized risk factors in ARVC/D such as syncope, nonsustained VT (NSVT), malignant family history, and inducibility at PVS.

Patients had to have successful implantation of an ICD that provided stored intracardiac electrograms and a follow-up period of at least 6 months after device implantation. Data of baseline clinical characteristics, including the results of noninvasive and invasive cardiac evaluation and implantation data, were collected in all patients. Decisions about device programming were made at the discretion of the patient’s clinical electrophysiologist at the enrolling center. For each patient, rate cutoff criteria for antitachycardia pacing and documented by stored intracardiac ECG data. Inappropriate interventions were defined as those triggered by a rapid ventricular rate resulting from supraventricular tachyrhythmias, sinus tachycardia, or device malfunction. Criteria for diagnosis of ventricular tachyrhythmias included morphology of intracardiac electrograms, acute onset of the tachycardia, and atrioventricular dissociation. VF or VT was defined as irregular or regular tachycardia with regard to polarity, amplitude, morphology, and sequence of intracardiac electrograms, with a mean cycle length of ≤240 milliseconds (ie, ≥250 bpm). VT was defined as regular tachycardia with a mean cycle length >240 milliseconds. All stored electrograms of arrhythmic events that triggered ICD therapy were classified as appropriate or inappropriate independently by 2 experienced electrophysiologists. The interobserver agreement was 100% for VF and VT with rates ≥250 bpm. Disagreement occurred in 5 arrhythmic episodes with rates <250 bpm; 3 of these episodes were classified by consensus as supraventricular triggering inappropriate ICD therapy and 2 as VTs.

Analysis of Survival Benefit of ICD Therapy

As previously reported, projected mortality curves were constructed with the first shock on episodes of VF/VT, which were used as a surrogate of arrhythmic SD. This was achieved by analysis of the stored ECGs of ICD shocks in response to VF/VT occurring during follow-up. The presumed benefit from ICD on survival was estimated by comparing actual patient survival rates with freedom from VF/VT episodes.

Definitions

Syncope was defined as a sudden transient loss of consciousness not requiring electric cardioversion for recovery. Syncope episodes were unrelated to extracardiac causes and occurred in the absence of documented ventricular arrhythmias and/or circumstances clearly leading to reflex-mediated changes in vascular tone or heart rate such as a micturition, defecation, cough, or other similar conditions. Syncope was classified as recurrent when ≥2 such episodes occurred. NSVT was defined as ≥3 consecutive ventricular premature beats with a rate >100 bpm that lasted <30 seconds that was documented during exercise testing or 24-hour Holter monitoring. Electric or VT storm was defined as the occurrence of VT or VF that resulted in 3 or more ICD interventions (shock or antitachycardia pacing) in a 24-hour period.

Statistical Analysis

The clinical variables analyzed were age at enrollment, follow-up, gender, family history of SD, NSVT, syncope, right precordial T-wave inversion, late potentials on signal-averaged ECG, diffuse RV involvement, angiographic RV end-diastolic volume, left ventricular dysfunction, arrhythmogenic drug therapy, and inducibility at PVS. Categorical differences between groups were evaluated by the χ² test. Differences between group means were compared by an unpaired t test. Results are expressed as range and mean ± SD. Event-free survival rates were estimated by the Kaplan-Meier method and compared by log rank. Univariate Cox regression
analysis identified baseline variables that were significantly associated with ICD therapy. Significantly associated variables ($P<0.15$) were integrated into multivariable analysis using Cox proportional-hazard models to identify independent predictors of any appropriate ICD interventions and shock therapy on VF/VfI. A value of $P<0.05$ was considered significant. Statistics were analyzed with SPSS version 17 (SPSS Inc, Chicago, Ill).

## Results

### Patient Characteristics

The study population consisted of 106 patients, 16 to 65 years (mean $35.6\pm18$ years) of age, whose clinical characteristics are summarized in Table 1. At the time of implantation, 99 of the 106 patients had no or mild functional limitation (New York Heart Association class I or II), and 7 had moderate to severe symptoms (New York Heart Association class III or IV). By design, no patients had previously experienced VF or sustained VT. The indication for prophylactic ICD therapy was based on 1 or more of the following risk factors: (1) history of premature SD in 1 or more first-degree or other relatives <50 years (49 patients, 46%), (2) NSVT on exercise testing and/or 24-hour ambulatory Holter ECG monitoring (56 patients, 53%), (3) prior syncope (42 patients, 40%) that occurred at rest or during ordinary activity in 31 and during moderate to intense effort in 11 (7 patients had recurrent syncope [ie, $\geq2$ episodes]), or (4) inducibility at PVS (40 of 67 patients who underwent electrophysiological study before ICD implantation, 60%). Patients were inducible to either sustained VT (26 patients, 65%) with a mean cycle length of 277±59 milliseconds (range, 220 to 405 milliseconds) or VF (14 patients, 35%).

A single-chamber ICD was implanted in 74 patients (70%), whereas 32 patients (30%) received a dual-chamber device. At the time of hospital discharge and/or at follow-up, 36 patients (34%) received concomitant antiarrhythmic drugs, including sotalol ($n=27$), amiodarone alone ($n=2$) or with $\beta$-blockers ($n=4$), and class I drugs ($n=3$), and 25 patients (24%) $\beta$-blockers.

### Outcome

During a mean follow-up of $58\pm31$ months (4.8 years) after ICD implantation, no deaths occurred. Of the 106 study patients, 25 (24%) had appropriate ICD interventions (including shock therapy on VF/VfI in 17) (Figure 1A), 20 (19%) had inappropriate ICD interventions, and 18 (17%) had device-related complications.

### Appropriate ICD Interventions

Twenty-five of 106 patients (24%) received a total of 224 appropriate device interventions for episodes of ventricular tachyarrhythmias. The mean cycle length of detected ventricular tachyarrhythmias was $264\pm48$ milliseconds. The average annual rate of appropriate ICD interventions for the overall study group was 4.8%. Ten patients had a single intervention, 8 had 2 to 5 interventions, and 7 had $>5$ interventions, including 2 patients with VT storm. The ICD interventions were defibrillation shocks in 18 patients, antitachycardia pacing in 3, and both in 4. Appropriate ICD interventions were preceded by symptoms in all but 2 patients (syncope in 14 patients, presyncope in 7, and palpitations in 2). The age at which the first appropriate intervention occurred ranged from 15 to 56 years (mean, $34\pm13$ years). The interval between implantation of the ICD and the initial appropriate intervention ranged from 5 to 66 months (mean, $14\pm23$ months).

Table 1 shows the correlation between patients with or without appropriate ICD interventions with respect to a series of clinical variables. Patients with appropriate ICD interventions were significantly younger ($32.1\pm10$ versus $36.7\pm8$ years; $P=0.04$) and more often had syncope (72% versus 30%; $P<0.001$), NSVT (72% versus 47%; $P=0.04$), and left ventricular dysfunction (44% versus 20%; $P=0.03$).

According to the analysis of the stored electrograms, 17 of 106 patients had 1 or more episodes of VF (11 patients), VfI (4 patients), or both (2 patients) that were successfully recognized and terminated by the device. The average annual rate of shocks on the first episode of VF/VfI was 3.3%. Shock

## Table 1. Characteristics of the Overall Sample and According to Appropriate ICD Therapy

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Overall Sample ($n=106$)</th>
<th>Appropriate ICD Therapy ($n=25$)</th>
<th>No Appropriate ICD Therapy ($n=81$)</th>
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<tbody>
<tr>
<td>Age at enrollment, y</td>
<td>35.6±18</td>
<td>32.1±10</td>
<td>36.7±8</td>
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<tr>
<td>Follow-up, mo</td>
<td>58±35</td>
<td>57.4±32</td>
<td>58.3±36</td>
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<tr>
<td>Male gender, n (%)</td>
<td>71 (67)</td>
<td>20 (80)</td>
<td>51 (63)</td>
</tr>
<tr>
<td>Family history of SD, n (%)</td>
<td>49 (46)</td>
<td>15 (60)</td>
<td>34 (42)</td>
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<tr>
<td>NSVT, n (%)</td>
<td>56 (53)</td>
<td>18 (72)</td>
<td>38 (47)</td>
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<tr>
<td>Syncope, n (%)</td>
<td>42 (39)</td>
<td>18 (72)</td>
<td>24 (30)</td>
</tr>
<tr>
<td>Right precordial T-wave inversion ($V_1-V_3$), n (%)</td>
<td>87 (82)</td>
<td>22 (88)</td>
<td>65 (80)</td>
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<tr>
<td>Late potentials on SAECG, n (%)</td>
<td>78 (74)</td>
<td>20 (80)</td>
<td>58 (72)</td>
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<tr>
<td>Diffuse RV involvement, n (%)*</td>
<td>98 (92)</td>
<td>24 (96)</td>
<td>74 (91)</td>
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<tr>
<td>Angiographic RV end-diastolic volume, mL/m²</td>
<td>110±18</td>
<td>111±17</td>
<td>110±20</td>
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<tr>
<td>LV dysfunction (EF &lt;55%), n (%)</td>
<td>27 (25)</td>
<td>11 (44)</td>
<td>16 (20)</td>
</tr>
<tr>
<td>Antiarrhythmic drug therapy, n (%)</td>
<td>65 (52)</td>
<td>18 (64)</td>
<td>47 (58)</td>
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<tr>
<td>Inducibility at PVS, n (%)</td>
<td>40/67 (60)</td>
<td>14/23 (61)</td>
<td>26/44 (59)</td>
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</tbody>
</table>

SAECG indicates signal averaged-ECG; LV left ventricular; and EF, ejection fraction.

*Diffuse RV involvement means severe regional ($\geq2$ RV regions) or global RV involvement (RV EF $\leq45$%).
therapy was preceded by symptoms of initial hemodynamic compromise in all patients (syncope in 11 patients and presyncope in 6). The interval between implantation and first ICD intervention triggered by VF/Vf ranged from 2 to 46 months (mean, 13 ± 19 months).

Of 42 patients with prior syncope, 18 (43%) experienced appropriate ICD interventions (against VT in 3 and VF/Vf in 15) during a mean follow-up of 56.6 ± 11 months (9.1% per year). During this time interval, 4 patients had a syncope recurrence (without any arrhythmia recorded on the device storage), which most likely was due to a neurocardiogenic mechanism. Of 40 asymptomatic patients with NSVT, 7 had appropriate ICD intervention (against VT in 5 and VF/Vf in 2) during a mean follow-up period of 57.3 ± 12 months (3.7% per year). None of the 27 asymptomatic patients, who had ICDs implanted because of isolated familial SD, experienced appropriate ICD discharges during a mean follow-up of 58.1 ± 18 months (0% per year), whereas 5 (19%) had inappropriate ICD therapies.

Figure 1B shows the difference between actual patient survival and VF/Vf-free patient survival. Compared with the 100% actual survival rate at 48 months of follow-up, VF/Vf-free survival rates were 91%, at 12 months, 87% at 24 months, 82% at 36 months, and 77% at 48 months of follow-up.

Predictors of ICD Therapy

Univariate and multivariable predictors of ICD therapy are listed in Tables 2 and 3. Univariate predictors of appropriate
ICD interventions were syncope (hazard ratio [HR], 3.82; 95% confidence interval [CI], 2.15 to 5.72; \( P = 0.008 \)) and NSVT (HR, 1.74; 95% CI, 1.35 to 3.19; \( P = 0.03 \)). On multivariable analysis, only syncope was found to be an independent predictor of appropriate ICD interventions (HR, 2.94; 95% CI, 1.83 to 4.67; \( P = 0.013 \)); NSVT reached borderline statistical significance (HR, 1.62; 95% CI, 0.96 to 2.62; \( P = 0.068 \)). Syncope was the only significant univariate (HR, 4.36; 95% CI, 2.86 to 7.91; \( P = 0.001 \)) and multivariable (HR, 3.16; 95% CI, 1.39 to 5.63; \( P = 0.005 \)) predictor of shock therapy on VF/VfL. No statistically significant synergism between any 2 clinical variables was observed.

Concomitant Antiarrhythmic Drug Therapy
At the time of first ICD intervention, 18 of the 25 patients (72%) who had appropriate ICD intervention were taking concomitant antiarrhythmic drug therapy, including sotalol (n=8), \( \beta \)-blockers (n=5), amiodarone (n=2), and propafenone (n=1). The incidence of appropriate ICD interventions did not differ between patients who did and did not receive antiarrhythmic drug therapy, regardless of clinical presentation (Table 1).

Electrophysiological Study
Of 40 patients who were inducible at PVS, 26 (65%) did not experience appropriate ICD interventions during the follow-up, whereas 8 of 27 (30%) noninducible patients had appropriate ICD interventions. The positive predictive value of PVS was 35% for any appropriate ICD intervention and 20% for shock therapy on VF/VfL, the negative predictive value was 70% and 74%, and the test accuracy was 49% and 42%. The type of ventricular tachyarrhythmia inducible at the time of electrophysiological study did not predict the occurrence of VF/VfL over the follow-up.

Inappropriate Interventions and Complications
Eighteen patients (17%) had device-related complications at the time of device implantation or during long-term follow-up, including pocket hematoma (n=4), lead repositioning (n=3), undersensing requiring an additional sep-
Ten patients (19%) received inappropriate ICD therapy. Reasons for inappropriate device interventions were sinus tachycardia (n = 9), supraventricular tachycardia/atrial fibrillation (n = 7), or oversensing (n = 4). Patients with inappropriate shock were significantly younger (32 ± 12 versus 36 ± 16 years; P = 0.02).

Discussion

The present study extended the previously published experience on ICD therapy in ARVC/D by addressing the outcome of patients with no prior spontaneous VT or VF who underwent prophylactic ICD implantation for the prevention of SD. The study results provide significant insights in identifying those patients with ARVC/D and no life-threatening ventricular arrhythmias in whom the probability of arrhythmic cardiac arrest over a long-term follow-up may be (or may not be) sufficiently high to justify ICD therapy.

Clinical Outcome

Over a long-term follow-up of 8 ± 5 years, one fourth of the study patients experienced a first episode of ventricular tachyarrhythmia that required ICD intervention despite antiarrhythmic drug therapy. This high cumulative incidence of appropriate ICD interventions indicates a significant risk of life-threatening ventricular arrhythmias over time in this ARVC/D patient population characterized by no prior sustained VT or VF and confirms the life-saving efficacy of prophylactic ICD therapy. It is noteworthy that this population represents a selected group of ARVC/D patients clinically estimated to have a high arrhythmic risk to justify prophylactic ICD therapy. Therefore, the reported rate of arrhythmic events does not necessarily correspond to the true arrhythmic risk of an unselected general cohort of ARVC/D patients, which is characterized by lower mortality rates. In patients with ARVC/D, a disease characterized by predominant RV involvement with a relatively preserved left ventricular function, not every episode of sustained ventricular tachyarrhythmia leads to SD; in particular, monomorphic VT may be well tolerated hemodynamically. For this reason, the estimate of the potential survival benefit of ICD in this study was limited to shock therapies on episodes of VF/Vf/II, which were identified by the analysis of the stored ECGs of the arrhythmic events triggering ICD therapy. In 17 of 25 patients, the arrhythmia-triggering ICD discharge was VF/Vf/II that may have been fatal without termination by the device. The annual rate of potentially “life-saving” shocks against VF/Vf/II was 3%. The Kaplan-Meier analysis of the incidence of ICD interventions that were triggered by VF/Vf/II suggests a significant improvement in survival through the follow-up period, with an actual total patient survival rate of 100% compared with a 77% VF/Vf/II survival rate at 48 months and an estimated benefit of ICD implantation of 23%.

However, the assumption that ICD shock against VF/Vf/II would have been life-saving in all cases may have led to an overestimation of the ICD survival benefit because even very rapid ventricular tachyarrhythmias may self-terminate before death. Accordingly, projected mortality curves based on freedom from life-threatening VF/Vf/II should be interpreted.

Table 2. Predictors of Appropriate ICD Interventions

<table>
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<tr>
<th>Variable</th>
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<th>Multivariable Analysis</th>
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<td>P</td>
<td>HR</td>
<td>95% CI</td>
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Abbreviations as in Table 1.

Table 3. Predictors of ICD Shock on VF/Vf/II

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<tr>
<th>Variable</th>
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<td></td>
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<td>P</td>
<td>HR</td>
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Abbreviations as in Table 1.
as an approximate estimation of the improved prognosis by prophylactic ICD in the ARVC/D study population.

### Syncope

The strongest predictor of ICD therapy in the study population of patients with ARVC/D and no prior arrhythmic cardiac arrest or sustained VT was a history of syncope. Patients with prior syncope had a 4-fold risk for subsequent episodes of potentially fatal VF/VfI. The importance of syncope as a risk factor for SD in ARVC/D was first reported by Marcus et al. in 2002 and later confirmed by other groups. The present study provides further evidence that syncope is a warning sign of increased arrhythmic risk in ARVC/D patients. The 9% annual incidence of appropriate ICD intervention among patients with prior syncope found in this study was comparable to that previously reported in patients who underwent device implantation because of a history of cardiac arrest or sustained VT. Moreover, of the 42 patients with prior syncope, only 4 had a syncope recurrence after ICD implantation, which occurred without a recorded arrhythmia and most likely was due to a neurocardiogenic mechanism.

Young individuals with genetic cardiomyopathies and/or ion channel disorders may suffer from vasovagal or, more widely, nonarrhythmic syncope, which makes differential diagnosis difficult and its prognostic value elusive. For instance, in patients with hypertrophic cardiomyopathy, several nonarrhythmic mechanisms such as reflex-mediated change in vascular tone or heart rate, left ventricular outflow tract obstruction, and supraventricular tachyarrhythmia may cause syncope. The results of the present study confirm that in ARVC/D patients most episodes of syncope are secondary to ventricular tachyarrhythmias and associated with a poor prognosis, similar to sustained VT or VF.

### Asymptomatic Patients

In the present study, therapy-based risk stratification analysis demonstrates that patients with ARVC/D but no previous cardiac arrest, sustained VT, or syncope have a low arrhythmic risk. Asymptomatic ARVC/D patients who received an ICD solely because of a family history of SD did not experience any appropriate ICD interventions over the follow-up. This is in agreement with previous studies showing that the majority of affected ARVC/D relatives are likely to have a benign course and that a sizable proportion of healthy gene carriers will not develop clinically significant disease owing to reduced disease penetrance.

Asymptomatic patients with NSVT presented a trend toward an increased arrhythmic risk. They had an overall rate of appropriate ICD intervention of 3.7%/y and a rate of appropriate ICD intervention against VF/VfI of 1.48%/y.

### Programmed Ventricular Stimulation

Conflicting data exist on the prognostic significance of PVS in patients with ARVC/D. Previous studies consisted mostly of ARVC/D patients with prior sustained VT or VF who inherently show a high prevalence of inducible ventricular arrhythmias at PVS and arrhythmia recurrences over time. The results of this study show that among ARVC/D patients with no prior spontaneous sustained VT or VF, preimplantation electrophysiological study is of limited value in identifying those individuals at risk of a first episode of lethal ventricular arrhythmia. The positive predictive value of PVS was 30% for any appropriate ICD interventions and 35% for potentially life-saving shock against VF/VfI. On the other hand, a negative PVS may not indicate better prognosis because approximately one third of noninducible patients experienced appropriate ICD interventions and approximately one fourth shock on potentially lethal arrhythmic events. Thus, the results of the present study do not support the routine use of PVS for risk stratification of ARVC/D patients without life-threatening ventricular arrhythmias.

This finding is in agreement with previous studies showing that electrophysiological study has a poor predictive value in identifying patients at risk for SD who may benefit of prophylactic ICD implantation. However, prophylactic ICD implantation may be not indicated in asymptomatic patients because of their unfavorable long-term outcome. Our study suggests that the subset of asymptomatic ARVC/D patients who underwent ICD implantation only because of a family history of SD may not benefit from ICD therapy. This result is particularly relevant for clinical management of the growing cohort of asymptomatic ARVC/D relatives and healthy gene carriers who are identified by cascade family screening. Demonstration of NSVT on 24-hour Holter monitoring and/or exercise testing in asymptomatic patients confers an increased risk of developing ventricular tachyarrhythmias during follow-up, although it does not predict the occurrence of potentially lethal VF/VfI. In this patient subgroup, the decision to implant an ICD should be made on a case-by-case basis and weighed against the significant risk of inappropriate interventions and complications.
Complications

The present study reports a 19% prevalence of inappropriate ICD interventions and a 17% prevalence of device-related complications during a mean follow-up period of ≈5 years. These findings are in agreement with the incidence of ICD-related complications and inappropriate interventions during long-term follow-up in young patients with ARVC/D or other genetic disorders such as hypertrophic cardiomyopathy and Brugada syndrome. It is noteworthy that one third of complications observed in our patients were lead related and required either lead repositioning or an additional septal lead because of undersensing. This may be explained by the peculiar ARVC/D pathobiology that leads to progressive loss of myocardium with fibrofatty replacement, also affecting the site of RV lead implantation.

Study Limitations

A prospective, randomized study design is difficult to perform in patients with ARVC/D because of practical limitations linked predominantly to relatively low disease prevalence and low event rate. Hence, the design of the present study was that of an observational survey of 6 collaborative medical centers, with potential limitations in patient selection, device programming, and arrhythmic risk stratification. There were no systematic criteria for ICD implantation, and the clinical decisions relative to risk status and indications to ICD therapy were made at each participating center by the local electrophysiologist using recognized risk factors in ARVC/D. Antitachycardia pacing protocols and detection rates for ICD shocks were not uniformly programmed, which introduces the potential for detection bias; ie, patients with lower programmed thresholds may have more sensitive settings for the detection and treatment of ventricular tachyarrhythmias. Nevertheless, in our study, most detected ventricular tachyarrhythmias were >190 bpm (mean cycle length, 264±48 milliseconds), a finding that lessens the potential impact of this potential bias. Although the study cohort was relatively large for ARVC/D, a small number of asymptomatic patients and outcomes were analyzed. The small number of events limits both the power to detect associations and the ability to control completely for all potential confounders in the multivariable models. This limitation is especially important with regard to factors not associated with ICD shock. Nonetheless, we believe that our study results and statistical analyses indicate important trends that are of clinical relevance for arrhythmic risk stratification and management of ARVC/D patients with no prior sustained VT or VF. Finally, survival benefit of ICD therapy was assessed by assuming that VF/VF would have been fatal in all cases without shock therapy. Because even very rapid ventricular tachyarrhythmias may self-terminate before death, the use of appropriate ICD shocks for VF/VF as a surrogate for SD may have led to an overestimation of survival benefit from ICD. Nonetheless, projected mortality curves based on freedom from life-threatening VF/VF allow some estimate of the improved prognosis by prophylactic ICD in our study population of ARVC/D patients.

Conclusions

Patients with ARVC/D and no previous VF or sustained VT have a significant risk of life-threatening ventricular arrhythmias during follow-up. Although ICD confers optimal protection against SD, economic costs and quality-of-life concerns, including psychological repercussions, risk for inappropriate shocks, and device-related complications, argue strongly against indiscriminate device implantation. Patients with prior episodes of syncope have the poorest prognosis and should be considered for prophylactic ICD implantation. ICD therapy may be not justified in asymptomatic patients with a family history of SD because of the favorable outcome, in addition to a significant risk of device-related complications and inappropriate discharges. These patients should be followed up by regular cardiac investigations for early recognition of symptoms, ventricular arrhythmias, or disease progression. Asymptomatic patients with NSVT have an intermediate arrhythmic risk, and the decision to implant an ICD needs to be individualized. PVS has limited accuracy in predicting appropriate ICD interventions and should not be used as a routine prognostic strategy. Further studies with larger number of patients and longer follow-up are needed to determine the long-term clinical outcome of asymptomatic ARVC/D patients and to confirm that their arrhythmic risk remains low over time as to justify not implanting an ICD.

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References

cardioverter-defibrillators in patients with arrhythmogenic right ventricular
8. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chairman B, Fromer M,
Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA,
Rodet DM, Silka MJ, Tracy C, Smith SC Jr., Jacobs AK, Adams CD,
JP, Page RL, Riegel B, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres
C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A,
Tangaro JL, Zamorano JL; American College of Cardiology/American
Heart Association Task Force; European Society of Cardiology Committee
for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC Guidelines for management
of patients with ventricular arrhythmias and the prevention of sudden
cardiac death: a report of the American College of Cardiology/American
Heart Association Task Force and the European Society of Cardiology
Committee for Practice Guidelines (Writing Committee to Develop
Guidelines for Management of Patients With Ventricular Arrhythmias
and the Prevention of Sudden Cardiac Death). developed in collaboration
with the European Heart Rhythm Association and the Heart Rhythm Society.
Circulation. 2006;114:e385–e484.
and risk stratification of arrhythmogenic right ventricular dysplasia/cardio-
10. McKenna WJ, Thieme G, Nava A, Fontaliran F, Blomstrom-Lundqvist C,
Fontaine G, Camerini F. Diagnosis of arrhythmogenic right ventricular
11. Credner SC, Klingenberg T, Mauss O, Sticherling C, Holmloer SH.
Electrical storm in patients with transvenous implantable cardioverter-
defibrillators: incidence, management and prognostic implications. J Am
NA III. Arrhythmogenic right ventricular dysplasia: clinical results with
13. Tavernier R, Gevaert S, de Sutter J, De Clercq A, Rottiers H, Jordaens L,
Hodgkinson KA, Parfrey PS, Bassett AS, Kupprion C, Drenckhahn J,
Norman MW, Thierfelder L, Stuckless SN, Dicks EL, McKenna WJ,
Connors SP. The impact of implantable cardioverter-defibrillator therapy
on survival in autosomal-dominant arrhythmogenic right ventricular cardi-
omopathy (ARVD5). J Am Coll Cardiol. 2005;45:400–408.
14. Blomstrom-Lundqvist C, Sabel KG, Olsson SB. A long term follow-up of
de Zulougâ C, Moncada E, Kerkorian G, Toumboul P. Prognostic and
evolution long terme de la dysplasie arhythmogene du ventricle droit.
16. Leclercq JF, Coulm P, Denjoy I, Maisonnblanche P, Cauchenez B,
Chouty F, Leenhardt A, Slam R. Long-term follow-up after sustained
monomorphic ventricular tachycardia: causes, pump failure and empiric
antiarrhythmic therapy that modify survival. Am Heart J. 1991;121:
1685–1692.
17. Marcus FI, Fontaine GH, Frank R, Guglielmi JJ, Reiter MJ. Long-term
follow-up in patients with arrhythmogenic right ventricular disease. Eur
18. Nava A, Bause B, Basso C, Muriago M, Rampazzo A, Villanov C,
Daliento L, Buia G, Corrado D, Danieli GA, Thiene G. Clinical profile
and long-term follow-up of 37 families with arrhythmogenic right vent-
20. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular
1988;318:129–133.
Tichnell C, James C, Russell SD, Judge DP, Abraham T, Spevak PJ,
Bluemke DA, Calkins H. Arhythmogenic right ventricular dysplasia: a
22. Spirito P, Autore C, Rapipezzi C, Bernabò P, Badalghacca R, Maron MS,
Bongioanni S, Cocomo F, Estes NA III, Bazillia CS, Biagini E, Quartera G,
Conte MR, Bruzzi P, Maron BJ. Syncope and risk of sudden death in
of antiarrhythmic drugs in patients with arrhythmogenic right ventricular
death: results in patients with inducible and noninducible ventricular
24. Wichter T, Breithardt G. Implantable cardioverter-defibrillator therapy
in arrhythmogenic right ventricular cardiomyopathy: a role for genotyping
25. Sen-Chowdhry S, Syrris P, McKenna WJ. Role of genetic analysis in the
management of patients with arrhythmogenic right ventricular dysplasia/

**CLINICAL PERSPECTIVE**

Arrhythmogenic right ventricular cardiomyopathy/dysplasia is an inheritable heart muscle disease with a natural history
that is related predominantly to sudden death, mostly in young people. There is general agreement that an implantable
cardioverter-defibrillator (ICD) is indicated in arrhythmogenic right ventricular cardiomyopathy/dysplasia patients who
survived an episode of ventricular fibrillation or sustained ventricular tachycardia. Whereas prophylactic ICD therapy in
patients with no history of sustained tachyarrhythmias or cardiac arrest is still an unsolved issue. There is a tendency to
implant an ICD once the disease has been diagnosed, regardless of symptoms or life-threatening ventricular arrhythmias.
Hence, a growing cohort of young arrhythmogenic right ventricular cardiomyopathy/dysplasia patients such as
asymptomatic relatives and healthy gene carriers who are identified by cascade family screening may undergo unnecessary
ICD implantations with significant economic costs and quality-of-life concerns. The present multicenter study assessed the
long-term outcome and determinants of ICD therapy in a large arrhythmogenic right ventricular cardiomyopathy/dysplasia
population with no prior ventricular fibrillation or sustained ventricular tachycardia. The study results suggest that ICD
implantation is as necessary in patients with a history of syncope as it is in those who suffer arrhythmic cardiac arrest.
However, prophylactic ICD implantation may not be justified in asymptomatic patients regardless of family history of
sudden death or results of programmed ventricular stimulation because of their favorable long-term outcome. Programmed
ventricular stimulation, traditionally used to stratify the risk of arrhythmogenic right ventricular cardiomyopathy/dysplasia
patients without spontaneous ventricular tachyarrhythmias, is of limited value in predicting appropriate ICD interventions
and should not be used as a routine prognostic strategy.
Prophylactic Implantable Defibrillator in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia and No Prior Ventricular Fibrillation or Sustained Ventricular Tachycardia

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