Outcome After Implantation of a Cardioverter-Defibrillator in Patients With Brugada Syndrome
A Multicenter Study–Part 2

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Background—Implantable cardioverter-defibrillator indications in Brugada syndrome remain controversial, especially in asymptomatic patients. Previous outcome data are limited by relatively small numbers of patients or short follow-up durations. We report the outcome of patients with Brugada syndrome implanted with an implantable cardioverter-defibrillator in a large multicenter registry.

Methods and Results—A total of 378 patients (310 male; age, 46±13 years) with a type 1 Brugada ECG pattern implanted with an implantable cardioverter-defibrillator (31 for aborted sudden cardiac arrest, 181 for syncope, and 166 asymptomatic) were included. Fifteen patients (4%) were lost to follow-up. During a mean follow-up of 77±42 months, 7 patients (2%) died (1 as a result of an inappropriate shock), and 46 patients (12%) had appropriate device therapy (5±5 shocks per patient). Appropriate device therapy rates at 10 years were 48% for patients whose implantable cardioverter-defibrillator indication was aborted sudden cardiac arrest, 19% for those whose indication was syncope, and 12% for the patients who were asymptomatic at implantation. At 10 years, rates of inappropriate shock and lead failure were 37% and 29%, respectively. Inappropriate shock occurred in 91 patients (24%; 4±4 shocks per patient) because of lead failure (n=38), supraventricular tachycardia (n=20), T-wave oversensing (n=14), or sinus tachycardia (n=12). Importantly, introduction of remote monitoring, programming a high single ventricular fibrillation zone (>210–220 bpm), and a long detection time were associated with a reduced risk of inappropriate shock.

Conclusions—Appropriate therapies are more prevalent in symptomatic Brugada syndrome patients but are not insignificant in asymptomatic patients (1%/y). Optimal implantable cardioverter-defibrillator programming and follow-up dramatically reduce inappropriate shock. However, lead failure remains a major problem in this population. (Circulation. 2013;128:1739-1747.)

Key Words: Brugada syndrome • death, sudden, cardiac • defibrillators, implantable

Brugada syndrome (BrS) is an arrhythmogenic disease characterized by an ECG pattern of right bundle-branch block, ST-segment elevation in the right precordial leads, and an increased risk of sudden cardiac arrest (SCA) as a result of polymorphic ventricular tachyarrhythmias or ventricular fibrillation (VF).1 Whereas the implantable cardioverter-defibrillator (ICD) is considered the main therapy in symptomatic patients, we2 and others3–7 have reported

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the low prevalence of arrhythmic events and high risk of complications in this young, otherwise healthy population. However, these studies were limited by the relatively small number of patients or short follow-up. We continued our initial registry in the same 14 centers to obtain a longer-term follow-up and to evaluate the evolution of ICD management in BrS patients.

Methods

Study Population
All patients diagnosed with BrS and implanted with an ICD in 14 centers between 1993 and 2005 were included in our initial study (group 1). We continued their follow-up and included all additional BrS patients implanted with an ICD up to December 2011 in the same 14 centers. Group 2 includes BrS patients implanted between 2006 and 2011. The diagnosis was made after an episode of aborted SCA, during evaluation of syncope, in asymptomatic patients with a suggestive ECG pattern recorded during routine examination, or as a consequence of familial screening after the diagnosis of BrS in a family member. This registry was approved by the institutional review committee, and the subjects gave informed consent.

Diagnosis, Clinical Data, and Electrophysiological Testing
Patients were included in this study only if they had a type 1 Brugada pattern on ECG at baseline on at least 1 occasion or after provocation with a class I antiarrhythmic drug. A type 1 ECG was defined as a prominent coved ST-segment elevation displaying J-wave amplitude or ST-segment elevation ≥0.2 mV at its peak followed by a negative T wave.8 The choice of class I drug was determined by its availability in the participating hospitals. Intravenous ajmaline (1 mg/kg body weight at a rate of 10 mg/min), flecainide (2 mg/kg body weight over 10 minutes with a maximum of 150 mg), or pilsicainide (1 mg/kg body weight over 10 minutes) was used. In addition, treadmill exercise testing and biochemical analysis excluded acute ischemia and metabolic or electrolyte disturbances. Echocardiography was performed to rule out underlying structural heart disease.

The following clinical data were collected in all 14 participating centers: circumstances of diagnosis, indication for ICD implantation, age at diagnosis, sex, family history of sudden cardiac death (before 45 years of age), results of pharmacological testing for unmasking the characteristic coved-type ECG pattern, and invasive electrophysiological study (EPS) when performed. Patients with a history of presumed arrhythmic syncope, documented sustained ventricular arrhythmia, or aborted SCA were considered symptomatic.

EPS indication evolved throughout the study period, and EPS was performed at the discretion of the electrophysiologist. A maximum of 3 ventricular extrastimuli were delivered from 2 ventricular sites unless an inducible ventricular arrhythmia was elicited at a previous step. Premature beats were started in late diastole, and coupling intervals were then reduced in 10- or 20-millisecond decrements to 200 milliseconds or until refractoriness was reached. This protocol did not use higher stimulus current or repetition of double and triple extrastimulation at the shortest coupling intervals. Inducible ventricular arrhythmia was defined as any ventricular arrhythmia lasting >30 seconds, causing syncope/circulatory collapse, or requiring intervention to be terminated. Therefore, patients with inducible, asymptomatic, nonsustained ventricular arrhythmia that terminated spontaneously before syncope were classified as noninducible. The minimum syncope workup included a careful patient history, a 12-lead ECG, echocardiography, a stress test, and Holter monitoring. Syncope classification was based mainly on clinical features in the absence of ECG monitoring during the syncopal event. An arrhythmic origin was suspected in the absence of (or brief) prodrome, the absence of a specific triggering circumstance, a brief loss of consciousness, a fast return to consciousness, or severe trauma.

Follow-Up
In the absence of symptoms or device therapy, patients were seen routinely every 3 to 6 months for clinical review and device interrogation, according to local practice, and every 6 to 12 months for patients with ICD remote monitoring capabilities. ICD programming was at the discretion of the referring electrophysiologists, but after our initial study in 2006,6 we recommended programming a single VF zone above 210 to 220 bpm.

In the event of a shock, the patient was seen at the ICD clinic within 24 hours, and the device was interrogated. Appropriate therapies were defined as shocks or antitachycardia pacing delivered for ventricular tachycardia (VT) or VF, and inappropriate shocks were defined as those delivered in the absence of ventricular arrhythmia. Only the first appropriate therapy, the first inappropriate shock, and the first lead failure were considered for analysis. Data were collected until December 2011. Follow-up was extended up to 6 months for patients who had been implanted from July to December 2011 to provide at least 6 months of follow-up for all patients.

Statistical Analysis
All quantitative variables were normally distributed according to the Shapiro-Wilk test except the delay between ICD implantation and lead failure. Data were expressed as mean±SD or as median (25th and 75th percentiles) for the delay between ICD implantation and lead failure. One-way ANOVA was performed to compare continuous variables. Two-by-two comparisons of quantitative variables were made with the Student t test. The χ² test was used to compare categorical variables. Comparison between Kaplan–Meier survival curves was made with the log-rank test. A value of P<0.05 was considered statistically significant.

To assess the contribution of baseline patient characteristics to the prediction of the likelihood of first appropriate therapy from the ICD and first lead failure during follow-up, multivariable Cox proportional hazard regression analysis was used. Only variables with a value of P<0.20 in univariable analysis were used for the multivariable analysis. For appropriate therapy, sex, age, symptoms, period of inclusion, family history of SCA, spontaneous type 1 ECG, positive EPS, and SCN5A mutation were tested in univariable analysis. Only symptoms and spontaneous type 1 ECG had a value of P<0.20. For lead failure, we tested the following parameters: age, sex, symptoms, family history of SCA, date of ICD implantation (before or after 2006), and type of ICD lead. Only family history of SCA and type of ICD leads had a value of P<0.20 in univariable analysis.

All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Clinical Characteristics and Indication for ICD Implantation
The percentage of BrS patients implanted with an ICD dropped over the years from 30% until 2005 (group 1) to 22% between 2006 and 2011 (group 2; P=0.001; Figure 1). Study population characteristics are summarized in Table 1 (378 patients; 82% male; mean age at diagnosis, 46±13 years). The vast majority of patients were white (91%), with Asian and black race accounting for 8% and 1% of patients, respectively. In 226 individuals (60%), a spontaneous type 1 ECG was present at baseline. In the remaining individuals, class I antiarrhythmic drug administration unmasked the diagnostic type 1 ECG. EPS was less likely to be used to risk stratify patients after 2005 (90% in group 1 versus 72% in group 2; P<0.001). An SCN5A mutation was found in 41 of 160 patients (26%) in whom the results of genetic testing were available. A family history of SCA was found in 135 patients (36%).
Before ICD implantation, 166 patients (44%) were asymptomatic, 181 patients (48%) previously had at least 1 episode of syncope with no clear extracardiac cause, and 31 patients (8%) had been resuscitated from SCA. Among the 166 asymptomatic patients, indications included (1) inducible ventricular arrhythmias at EPS (n=139), (2) no inducible ventricular arrhythmia but a family history of BrS and SCA (n=21), (3) spontaneous nonsustained ventricular arrhythmia (n=3), and (4) a spontaneous type 1 Brugada pattern along with electrophysiologist or patient preference for ICD (n=3; Figure 2). ICD indications dramatically changed over time (Table 1), with fewer asymptomatic patients and more patients with syncope implanted. Whereas asymptomatic BrS patients represented 52% of patients with ICD before 2006 (group 1), their proportion dropped to 33% since 2006 (group 2; P<0.001) mainly as a result of the decrease in the number of EPSs performed (198 in group 1 versus 113 in group 2; P<0.001).

At implantation, R-wave amplitude was >5 mV in 330 of 366 patients (12 were missing data), and small-diameter recalled ICD leads (Medtronic Sprint Fidelis or St. Jude Medical Riata) were used in 82 of 378 patients (22%).

**Outcome**

During a mean follow-up of 77±42 months (median, 76 months; range, 6–220 months) after ICD implantation, 15 patients (4%) were lost to follow-up, and 7 patients (1.8%) died. Mean age at death was 59±12 years, with causes of death including malignancy (n=3), suicide (n=2), severe trauma without preceding syncope (n=1), and inappropriate ICD discharge resulting from lead failure (n=1). During follow-up, a mean of 1.5±0.6 (25th–75th percentile, 1–4) ICDs per patient were implanted. Twelve percent of the patients (n=46) experienced appropriate therapy. Its rate differed according to ICD indication (aborted SCA, 39%–6.9% per year; syncope, 12%–2% per year; and asymptomatic, 7%–1% per year; P<0.001; Figure 3), and the mean delay to first therapy after ICD implantation was much shorter for patients with previous aborted SCA (18 months) compared with patients with previous syncope (4 years) or asymptomatic patients (4 years; Table 2). The rate of appropriate therapy 10 years after ICD implantation was 48% in patients with aborted SCA, 19% in patients with syncope, and 12%

### Table 1. Characteristics of the Brugada Syndrome Population According to the Period of ICD Implantation

<table>
<thead>
<tr>
<th></th>
<th>Group 1, Initial Population (n=220)</th>
<th>Group 2, Patients Implanted Since 2006 (n=158)</th>
<th>P Value</th>
<th>Total (n=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>183 (83)</td>
<td>127 (80)</td>
<td>0.48</td>
<td>310 (82)</td>
</tr>
<tr>
<td>Age, y</td>
<td>46±12</td>
<td>47±14</td>
<td>0.40</td>
<td>46±13</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>205 (93)</td>
<td>138 (87)</td>
<td></td>
<td>343 (91)</td>
</tr>
<tr>
<td>Asian</td>
<td>12 (5)</td>
<td>18 (11)</td>
<td>0.11</td>
<td>30 (8)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td></td>
<td>5 (1)</td>
</tr>
<tr>
<td>ICD indication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aborted SCA</td>
<td>18 (8)</td>
<td>13 (8)</td>
<td></td>
<td>31 (8)</td>
</tr>
<tr>
<td>Syncope</td>
<td>88 (40)</td>
<td>93 (59)</td>
<td>0.001</td>
<td>181 (48)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>114 (52)</td>
<td>52 (33)</td>
<td></td>
<td>166 (44)</td>
</tr>
<tr>
<td>Family history of SCA, n (%)</td>
<td>91 (41)</td>
<td>45 (25)</td>
<td>0.001</td>
<td>135 (36)</td>
</tr>
<tr>
<td>Spontaneous type 1 ECG, n (%)</td>
<td>137 (62)</td>
<td>89 (56)</td>
<td>0.25</td>
<td>226 (60)</td>
</tr>
<tr>
<td>Number of patients with EPS, n (%)</td>
<td>198 (90)</td>
<td>113 (72)</td>
<td>&lt;0.001</td>
<td>311 (82)</td>
</tr>
<tr>
<td>ICD with remote monitoring, n (%)</td>
<td>69 (31)</td>
<td>78 (49)</td>
<td>&lt;0.001</td>
<td>147 (39)</td>
</tr>
<tr>
<td>Patients with genetic test, n (%)</td>
<td>102 (46)</td>
<td>58 (37)</td>
<td></td>
<td>160 (42)</td>
</tr>
<tr>
<td>SCN5A mutation</td>
<td>31 (30)</td>
<td>10 (17)</td>
<td>0.17</td>
<td>41 (26)</td>
</tr>
</tbody>
</table>

Values of P<0.05 were significant. Group 1: patients with Brugada syndrome from our initial study implanted until 2005; group 2, patients with Brugada syndrome implanted with an ICD since 2006 in the same 14 centers. EPS indicates electrophysiological study; ICD, implantable cardioverter-defibrillator; and SCA, sudden cardiac arrest.
in asymptomatic patients (Table 3). First appropriate shock could occur as late as 13 years after initial ICD implantation. Eleven patients had only 1 shock; 24 patients had 2 to 10 shocks. Eleven patients (24% of patients with shocks) presented with an arrhythmic storm (≥3 episodes within 24 hours) and were treated with quinidine (n=6) or ablation (5 patients) after short-term use of isoproterenol in 4 patients. They had a mean of 13 ± 5 shocks compared with 3 ± 2 for those without arrhythmic storm (P<0.001).

Five patients (11% of patients with appropriate ICD therapies) had therapies for monomorphic VT (4 shocks and 1 antitachycardia pacing; mean VT cycle length, 280 ± 47 milliseconds). The patient with VT terminated by antitachycardia pacing suffered myocardial infarction between BrS diagnosis and VT. Forty-one patients had appropriate shocks for polymorphic VT or VF. Of note, 11 patients experienced nonsustained polymorphic VT/VF that did not result in ICD therapy. Three patients with self-terminating polymorphic VT/VF episodes never had any ICD therapy (Figure 4). In 6 patients, nonsustained polymorphic VT/VF occurred during sleep, and no symptoms were noted. The 5 remaining patients experienced lightheadedness/near syncope (n=3) or syncope (n=2). In terms of antiarrhythmic drug therapy, 13 patients were on quinidine (6 after arrhythmic storm, 2 for atrial fibrillation). Once the quinidine blood level was within therapeutic range (up to 600 mg of hydroxyquinidine twice daily), no patient had ventricular arrhythmia recurrence during follow-up. One patient had incomplete ablation owing to the absence of premature ventricular contractions and bleeding during pericardial access that limited the epicardial part of the ablation, but he was subsequently well controlled on quinidine therapy. The other 7 patients (5 patients with arrhythmic storm) with ablation did not have recurrence in the absence of any treatment.

Of the 12 asymptomatic patients who received an ICD and subsequently experienced appropriate therapies, 8 had a spontaneous type 1 Brugada ECG pattern at baseline, and all but 1 patient had inducible ventricular arrhythmia at EPS. Six had a family history of SCA before 45 years of age. All these patients were included before 2006 (initial study).

Figure 2. Baseline ECG of the 3 asymptomatic patients (A, B, and C) implanted because of 12-lead Brugada pattern and patient or physician preference.

Figure 3. Kaplan–Meier curve of appropriate shock depending on implantable cardioverter-defibrillator indication. SCA indicates sudden cardiac arrest.
Of note, 10 other patients (2.6%) with lead failure and subsequent extraction/device deactivation were not reimplanted because of physician or patient decision. Seven were asymptomatic at the time of initial ICD implantation and had received an ICD for positive EPS (n=5) or family history of SCA (n=2); the remaining 3 patients had been implanted for syncope. All 10 patients were still alive 44±33 months later.

In multivariable analysis, the only factor predictive of appropriate device discharge was the presence of symptoms before implantation (syncope: hazard ratio, 2.460; 95% confidence interval, 1.169–5.174; resuscitated SCA: hazard ratio, 10.149; 95% confidence interval, 4.364–23.607). Spontaneous type 1 ECG, age, sex, and family history of SCA were not predictive in this selected population.

Complications of ICD
Complications after hospital discharge for ICD implantation occurred in 135 patients (36%). The most common complication was inappropriate shock (n=91), followed by lead failure (n=60). Nine patients had infection in relation to the ICD, endocarditis (n=3) or ICD pocket infection (n=6), that required lead extraction in all (surgical approach in 1 patient) in addition to intravenous antibiotic therapy. Nine patients suffered from lead dislodgement or pocket hematoma, requiring specific reintervention in 3 patients. Five patients had pericardial effusion treated by pericardiocentesis. Severe depression was diagnosed in 5 patients, leading to suicide in 2 patients. Five patients had other types of complications: premature ICD failure caused by electric arc (n=1), upper-limb phlebitis (n=1), pulmonary embolism 2 weeks after ICD implantation (n=1), and transient stroke in patients with patent foramen ovale (n=2; a few days after lead extraction in 1 and several months after implantation in 1 patient whose ICD lead was inadvertently placed in the left ventricle through the patent foramen ovale). Fifty-one patients had their ICD changed prematurely: 50 because of lead failure and 1 because of an electric arc that shorted out the ICD.

Inappropriate ICD Therapy
Inappropriate shocks occurred in 91 patients (24%; mean, 3.8±4.2 shocks per patient) 35±31 months after ICD implantation. The rate of events after ICD implantation is presented in Table 3. The characteristics and outcome of the Brugada Syndrome population according to ICD indication are shown in Table 2.

Table 2. Characteristics and Outcome of the Brugada Syndrome Population According to ICD Indication

<table>
<thead>
<tr>
<th></th>
<th>Aborted SCA (n=31)</th>
<th>Syncope (n=181)</th>
<th>Asymptomatic (n=166)</th>
<th>P Value Between the 3 Groups</th>
<th>Total (n=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43±13</td>
<td>47±13</td>
<td>47±12</td>
<td>0.30</td>
<td>46±13</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>29 (94)</td>
<td>141 (78)</td>
<td>140 (84)</td>
<td>0.07</td>
<td>310 (82)</td>
</tr>
<tr>
<td>Familial history of SCA, n (%)</td>
<td>6 (19)</td>
<td>43 (24)</td>
<td>86 (52)</td>
<td>&lt;0.001</td>
<td>135 (36)</td>
</tr>
<tr>
<td>Spontaneous type 1 ECG, n (%)</td>
<td>23 (74)</td>
<td>111 (61)</td>
<td>92 (55)</td>
<td>0.12</td>
<td>226 (60)</td>
</tr>
<tr>
<td>Patients with EPS, n</td>
<td>15</td>
<td>145</td>
<td>150</td>
<td>0.004</td>
<td>310</td>
</tr>
<tr>
<td>Inducible at EPS, n (%)</td>
<td>8 (53)</td>
<td>90 (62)</td>
<td>130 (87)</td>
<td>&lt;0.001</td>
<td>228 (76)</td>
</tr>
<tr>
<td>Remote monitoring, n (%)</td>
<td>8 (26)</td>
<td>74 (41)</td>
<td>65 (39)</td>
<td>0.28</td>
<td>147 (39)</td>
</tr>
<tr>
<td>Mean follow-up, mo</td>
<td>67±49</td>
<td>71±44</td>
<td>85±36</td>
<td>0.04</td>
<td>77±42</td>
</tr>
<tr>
<td>Patients with appropriate shocks n, (%)</td>
<td>12 (39)</td>
<td>22 (12)</td>
<td>12 (7)</td>
<td>&lt;0.001</td>
<td>46 (12%)</td>
</tr>
<tr>
<td>Mean delay to first shock (minimum–maximum)</td>
<td>18±20 mo (2–54 mo)</td>
<td>47±46 mo (8–156 mo)</td>
<td>45±36 mo (27–125 mo)</td>
<td>&lt;0.001</td>
<td>39±39 mo (8–156 mo)</td>
</tr>
<tr>
<td>Mean shocks, n</td>
<td>5.4±5.5</td>
<td>5.4±5.8</td>
<td>4.5±4.7</td>
<td>0.91</td>
<td>5.2±5.3</td>
</tr>
<tr>
<td>Patients with inappropriate shocks, n (%)</td>
<td>6 (19)</td>
<td>38 (21)</td>
<td>47 (28)</td>
<td>0.23</td>
<td>91 (24)</td>
</tr>
<tr>
<td>Mean delay to first shock, mo</td>
<td>33±36</td>
<td>40±32</td>
<td>32±30</td>
<td>0.04</td>
<td>35±31</td>
</tr>
<tr>
<td>Mean shocks, n</td>
<td>3.7±3.8</td>
<td>4.8±5.3</td>
<td>3±3</td>
<td>0.18</td>
<td>3.8±4.2</td>
</tr>
<tr>
<td>R-wave amplitude at implantation &lt;5 mV, n (%)</td>
<td>3/30 (10)</td>
<td>15/178 (8)</td>
<td>18/158 (11)</td>
<td>0.66</td>
<td>36/366 (10)</td>
</tr>
<tr>
<td>Lead failure, n (%)</td>
<td>3 (10)</td>
<td>29 (16)</td>
<td>28 (17)</td>
<td>0.60</td>
<td>60 (16)</td>
</tr>
<tr>
<td>ICD explantation without reimplantation during follow-up, n (%)</td>
<td>0 (0)</td>
<td>3 (1.6)</td>
<td>7 (4)</td>
<td>0.21</td>
<td>10 (2.6)</td>
</tr>
<tr>
<td>Lost to follow-up, n</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>0.76</td>
<td>15</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>0 (0)</td>
<td>3 (1.6)</td>
<td>4 (2.4)</td>
<td>0.64</td>
<td>7 (1.8)</td>
</tr>
</tbody>
</table>

Table 3. Rate of Events After ICD Implantation

<table>
<thead>
<tr>
<th>Year</th>
<th>Aborted SCA</th>
<th>Syncope</th>
<th>Asymptomatic</th>
<th>Inappropriate Shock Rate, %</th>
<th>Lead Failure Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>3</td>
<td>1</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>6</td>
<td>2</td>
<td>13</td>
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<tr>
<td>3</td>
<td>36</td>
<td>7</td>
<td>4</td>
<td>15</td>
<td>5</td>
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<tr>
<td>4</td>
<td>41</td>
<td>10</td>
<td>6</td>
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<td>7</td>
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<td>5</td>
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<td>23</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>19</td>
<td>12</td>
<td>37</td>
<td>29</td>
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</table>

TOTAL for R-wave amplitude is 366 instead of 378 because data are missing for 12 patients. EPS indicates electrophysiological study; ICD, implantable defibrillator-cardioverter; and SCA, sudden cardiac arrest.
implantation with a risk at 10 years of 37% (Table 3). However the rate of inappropriate shocks decreased significantly after 2005 (Figure 5). Remote monitoring was used in 147 patients (39%) with use increasing since 2006 (31% in group 1 versus 49% in group 2; \( P<0.001 \)). In the subgroup of patients with lead failure, remote monitoring significantly decreased the occurrence of inappropriate shock from 91% to 44% (\( P<0.001 \)). Reasons for inappropriate shocks were lead dysfunction (n=38), supraventricular arrhythmias (n=20), T-wave oversensing (n=14), sinus tachycardia (n=12), and others (n=7). Two patients developed VF as a result of an inappropriate shock that could not be terminated by the device because of lead failure. One patient survived owing to prompt resuscitation maneuvers, but the second patient died.

Inappropriate shocks occurred in only 2 of 69 patients (2.3%; 0.7%/y) who had a combination of R-wave amplitude >5 mV at implantation, a long number of interval to detect duration, high VF rate (>210 to 220 bpm), and remote monitoring capabilities versus 3.7%/y in the general study population.

**Lead Failure**

Sixty patients (16%) experienced lead failure 56 months (25th–75th percentile, 36–72 months) after ICD implantation (Figure 6). Eighty-two patients (22%) had leads involved in a device recall or advisory (St. Jude Medical Riata or Medtronic Sprint Fidelis). They accounted for 27% (16 of 60) of lead failures. In this particular population (young and active), ICD leads not involved in a recall process also had a high risk of failure (Figure 6). Risk of lead failure increased dramatically 2 years after implantation up to a risk of 29% at 10 years (Table 3). No parameters (age, sex, symptoms, date of implantation, or presence of Sprint Fidelis/Riata leads) were found to be predictive of lead failure in univariable analysis.

**Discussion**

Six years after ICD implantation, BrS patients implanted with an ICD have twice the rate of inappropriate shock (24%) compared with appropriate shock (12%) with an overall complication rate of 36%. A major reason is a 29% risk of lead failure 10 years after implantation in this young otherwise healthy population (Figure 6). These results and the results of the France, Italy, Netherlands, Germany BrS Registry ('FINGER) provide important data to assist in patient counseling before ICD implantation in the setting of BrS.

Another finding is the evolution in the management of these patients since our initial work. The overall ICD implantation rate decreased in BrS patients from 30% during our initial study (group 1) to 22% since then (group 2; \( P=0.001 \)). This was
particularly true in asymptomatic patients (Table 1). However, we are still lacking tools to better risk stratify asymptomatic patients in whom the utility of EP study is questionable. Of note, none of our asymptomatic patients implanted since 2006 had appropriate shock. Currently, ICD implantation in asymptomatic patients is a case-by-case decision with a multifactorial approach involving an informed consent discussion with the patient. Although the risk for asymptomatic BrS patients is low, it is not insignificant (0.81%/y in patients with spontaneous type 1 ECG and 0.35%/y in patients with only induced type 1 pattern), and the consequence of not implanting an ICD in an asymptomatic patient who subsequently goes on to develop VF is extreme. In the subgroup of patients from Bordeaux (n=329; 91 with an ICD, 238 without), 2 asymptomatic subjects with Brugada pattern diagnosed during the period of the study but not implanted with an ICD died suddenly. The first patient was a 21-year-old man diagnosed after an ajmaline test because of familial BrS screening. He had a negative EPS (2 sites, 2 cycles, 3 extrastimuli down to 200 milliseconds) but died suddenly during his sleep 8 months later. The second patient, a 56-year-old asymptomatic man, underwent ajmaline test after a routine preoperative ECG performed before surgery showed a type 2 ECG pattern. He had no family history of SCA and did not undergo EPS. He died suddenly during sleep 16 months later. No autopsy was performed on either patient.

Even in patients with syncope, the decision to implant an ICD can be difficult because nonarrhythmic syncope is...
present in this young population. In a recent study,17 4 of 23 BrS patients with ICD implantation for suspected arrhythmic syncpe subsequently developed recurrent syncpe without arrhythmia on the ICD log. In a BrS patient with syncpe for whom the clinical history is not typical of an arrhythmic origin, an implantable loop recorder may be helpful. This would allow continued surveillance for ventricular arrhythmia but would avoid committing the patient to the potential complications of long-term ICD therapy, with the understanding, however, that the patient would remain unprotected during this monitoring period. To make this decision even more challenging, nonsustained polymorphic VT/VF was recorded on the ICD log in 11 patients from our study population who either were asymptomatic or simply complained of lightheadedness (Figure 4). Because of the complexity of the risk/benefit analysis, we strongly feel that decisions on ICD implantation in BrS patients should be performed at experienced centers and after a thorough discussion with the patient and family.

Owing to the results of our initial study, we also modified ICD programming with a single VF zone above 210 to 220 bpm, which helped to reduce the inappropriate shock rate (Figure 5). As recently demonstrated in Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT), such programming was associated not only with a reduction in inappropriate therapy but also with a reduction in all-cause mortality in patients with structural heart disease.18 Veltmann et al18 also showed that programming a single high-rate VF zone was safe and could prevent inappropriate therapy for BrS patients. Because monomorphic VT was recorded in 5 patients, a monitor zone from 180 bpm to the VF zone may be helpful. Importantly, patients with good implantation parameters (R-wave amplitude >5 mV at implantation), optimal programming (long interval to detection duration, single high VF zone >210–220 bpm), and close follow-up with remote monitoring had a low rate of inappropriate shock (0.7%/y compared with 3.7%/y in the general BrS population).

The other evolution that likely explains the decrease in inappropriate shock rate since 2006 is the incorporation of remote monitoring (Table 1) for the early detection of ICD lead failure or malfunction.5 It has the potential to reduce the morbidity associated with inappropriate shocks and may even prevent ICD-related death (as occurred in 1 of our patients and as described in the literature).16–18

An increasing challenge is the strategy to manage patients after lead failure and extraction. Extrapolation of the lead failure rates seen in Figure 6 indicates that patients implanted with an ICD in their 40s will have an important risk of lead failure during their life (life expectancy >30–40 years at implantation). The rate of standard ICD lead failure remains high not just in the small-diameter recalled leads (Figure 6). In case of lead failure, should we just reimplant a new ICD system as we often do simply on the basis of the initial decision to implant? One alternative for reimplantation could be the use of a recently developed subcutaneous ICD,19 but this also is not without risk of complications,20 and we currently have only short-term follow-up data on the safety and efficacy of this device. Another alternative is not to reimplant in certain patients (especially asymptomatic patients without ventricular arrhythmia recorded by the ICD log during an extended follow-up period), as was the case for 10 patients (2.6%) in our series. All 10 patients are still alive without symptoms after a mean of 44±33 months after ICD system extraction or deactivation. However, the long-term safety of this strategy is unknown. In our series, the first appropriate ICD therapy could occur as late as 13 years after ICD implantation. We now consider not reimplating an ICD in asymptomatic BrS patients without ventricular arrhythmia during follow-up who do not have persistent spontaneous type 1 Brugada pattern ECG. This strategy requires a case-by-case analysis after a review of the risks and benefits of reimplantation or not with the patient and family.

In patients with arrhythmic risk who refuse ICD/lead implantation, quinidine therapy may be an option because it is extremely effective in preventing VF recurrence21 when blood concentration is within the therapeutic range.

Finally, the psychological and social impacts of ICD are often underestimated. In this registry, 2 patients committed suicide, and 3 others suffered from severe depression. The social impact of ICD implantation is particularly important in young patients with implications for employment.22 Psychological evaluation before ICD implantation may be valuable in identifying more fragile patients requiring closer follow-up.

**Study Limitations**

This is a retrospective study, and the population included was identified from 14 different centers. Although every effort was made to collect the data in a uniform and thorough manner, some measurement bias may be present.

**Conclusions**

In this large BrS population (only 4% of patients were lost to follow-up), rates of appropriate shock at 5 and 10 years are 48% and 48% for patients implanted because of aborted SCA, 11% and 19% for those with syncope, and 6% and 12% for asymptomatic patients. Optimal ICD programming and follow-up dramatically reduce inappropriate shock rate. However, lead failure remains a major problem in this population (29% at 10 years).

**Disclosures**

None.

**References**


CLINICAL PERSPECTIVE

Although the risk of appropriate implantable cardioverter-defibrillator therapy is important in patients with Brugada syndrome, the risk of inappropriate therapy is even more concerning. The main issue remains lead failure, which occurs in up to 25% of patients at 10 years. As a consequence, the risk of inappropriate therapy is not negligible (1% per year), and follow-up implantable cardioverter-defibrillator (with remote monitoring capabilities) reduces the risk of inappropriate shock.
Outcome After Implantation of a Cardioverter-Defibrillator in Patients With Brugada Syndrome: A Multicenter Study–Part 2


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